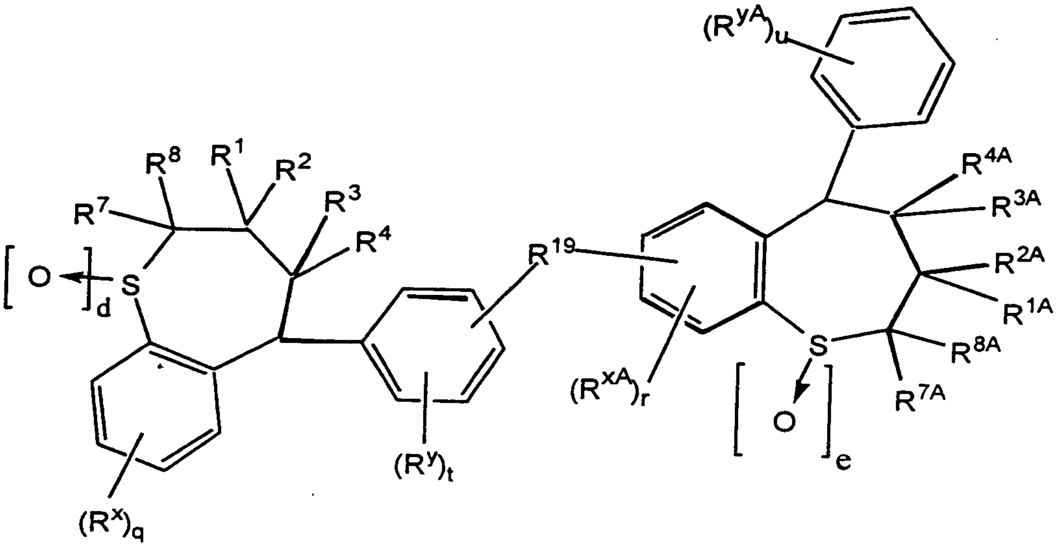


(V)

In any of the dimeric or multimeric structures discussed immediately above, benzothiepine compounds of the present invention can be used alone or in various combinations.

In any of the compounds of the present invention, R^1 and R^2 can be ethyl/butyl or butyl/butyl.

In another aspect, the present invention provides a pharmaceutical composition for the prophylaxis or treatment of a disease or condition for which a bile acid transport inhibitor is indicated, such as a hyperlipidemic condition, for example, atherosclerosis. Such compositions comprise any of the compounds disclosed above, alone or in combination, in an amount effective to reduce bile acid levels in the blood, or to reduce transport thereof across digestive system membranes, and a pharmaceutically acceptable carrier, excipient, or diluent.

In a further aspect, the present invention also provides a method of treating a disease or condition in mammals, including humans, for which a bile acid transport inhibitor is indicated, comprising administering to a patient in need thereof a compound of the present invention in an effective amount in unit dosage form or in divided doses.

In yet a further aspect, the present invention also provides processes for the preparation of compounds of the present invention.

Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed dscription and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will beomce apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the emobodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

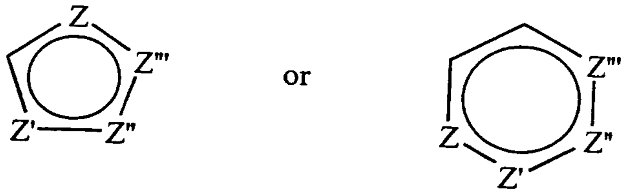
Definitions

In order to aid the reader in understanding the following detailed description, the following definitions are provided:

"Alkyl", "alkenyl," and "alkynyl" unless otherwise noted are each straight chain or branched chain hydrocarbons of from one to twenty carbons for alkyl or two to twenty carbons for alkenyl and alkynyl in the present invention and therefore mean, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl respectively and isomers thereof.

"Aryl" means a fully unsaturated mono- or multi-ring carbocyle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

"Heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms can be replaced by N, S, P, or O. This includes, for example, the following structures:



wherein Z, Z′, Z″ or Z‴ is C, S, P, O, or N, with the proviso that one of Z, Z′, Z″ or Z‴ is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z′, Z″ or Z‴ only when each is C.

The term "heteroaryl" means a fully unsaturated heterocycle.

In either "heterocycle" or "heteroaryl," the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

The term "quaternary heterocycle" means a heterocycle in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heterocycle to the molecule of interest can be at a heteroatom or elsewhere.

The term "quaternary heteroaryl" means a heteroaryl in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heteryaryl to the molecule of interest can be at a heteroatom or elsewhere.

The term "halogen" means a fluoro, chloro, bromo or iodo group.

The term "haloalkyl" means alkyl substituted with one or more halogens.

The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to ten carbon atoms, and wherein any ring can contain one or more double or triple bonds. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepine.

The term "diyl" means a diradical moiety wherein said moiety has two points of attachment to molecules of interest.

The term "oxo" means a doubly bonded oxygen.

The term "polyalkyl" means a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "polyether" means a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "polyalkoxy" means a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "cycloaklylidene" means a mono- or multi-ringed carbocycle wherein a carbon within the ring structure is doubly bonded to an atom which is not within the ring structures.

The term "carbohydrate" means a mono-, di-, tri-, or polysaccharide wherein the polysaccharide can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan.

The term "peptide" means polyamino acid containing up to about 100 amino acid units.

The term "polypeptide" means polyamino acid containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid untis, most preferably from about 100 amino acid units to about 500 amino acid units.

The term "alkylammoniumalkyl" means a NH_2 group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.

The term "triazolyl" includes all positional isomers. In all other heterocycles and heteroaryls which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocycles and heteroaryls.

The term "sulfo" means a sulfo group, $-SO_3H$, or its salts.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

The term "arylalkyl" means an aryl-substituted alkyl radical such as benzyl. The term "alkylarylalkyl" means an arylalkyl radical that is substituted on the aryl group with one or more alkyl groups.

The term "heterocyclylalkyl" means an alkyl radical that is substituted with one or more heterocycle groups. Preferable heterocyclylalkyl radicals are "lower heterocyclylalkyl" radicals having one or more heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

The term "heteroarylalkyl" means an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one or more heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

The term "quaternary heterocyclylalkyl" means an alkyl radical that is substituted with one or more quaternary heterocycle groups. Preferable quaternary heterocyclylalkyl radicals are "lower quaternary heterocyclylalkyl" radicals having one or more quaternary heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

The term "quaternary heteroarylalkyl" means an alkyl radical that is substituted with one or more quaternary heteroaryl groups. Preferable quaternary heteroarylalkyl radicals are "lower quaternary heteroarylalkyl" radicals having one or more quaternary heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

The term "alkylheteroarylalkyl" means a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are "lower alkylheteroarylalkyl" radicals with alkyl portions having one to ten carbon atoms.

The term "alkoxy" an alkyl radical which is attached to the remainder of the molecule by oxygen, such as a methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and *tert*-butoxy.

The term "carboxy" means the carboxy group, $-CO_2H$, or its salts.

The term "carboxyalkyl" means an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are "lower carboxyalkyl" radicals having one or more carboxy groups attached to an alkyl radical having one to six carbon atoms.

The term "carboxyheterocycle" means a heterocycle radical that is substituted with one or more carboxy groups.

The term "carboxyheteroaryl" means a heteroaryl radical that is substituted with one or more carboxy groups.

The term "carboalkoxyalkyl" means an alkyl radical that is substituted with one or more alkoxycarbonyl groups. Preferable carboalkoxyalkyl radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical having one to six carbon atoms.

The term "carboxyalkylamino" means an amino radical that is mono- or di-substituted with carboxyalkyl. Preferably, the carboxyalkyl substituent is a "lower carboxyalkyl" radical wherein the carboxy group is attached to an alkyl radical having one to six carbon atoms.

The term "active compound" means a compound of the present invention which inhibits transport of bile acids.

When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

The term "a bile acid transport inhibitor" means a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

Compounds

The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the compounds of the present invention.

The compounds of the present invention also include tautomers.

The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

Compound Syntheses

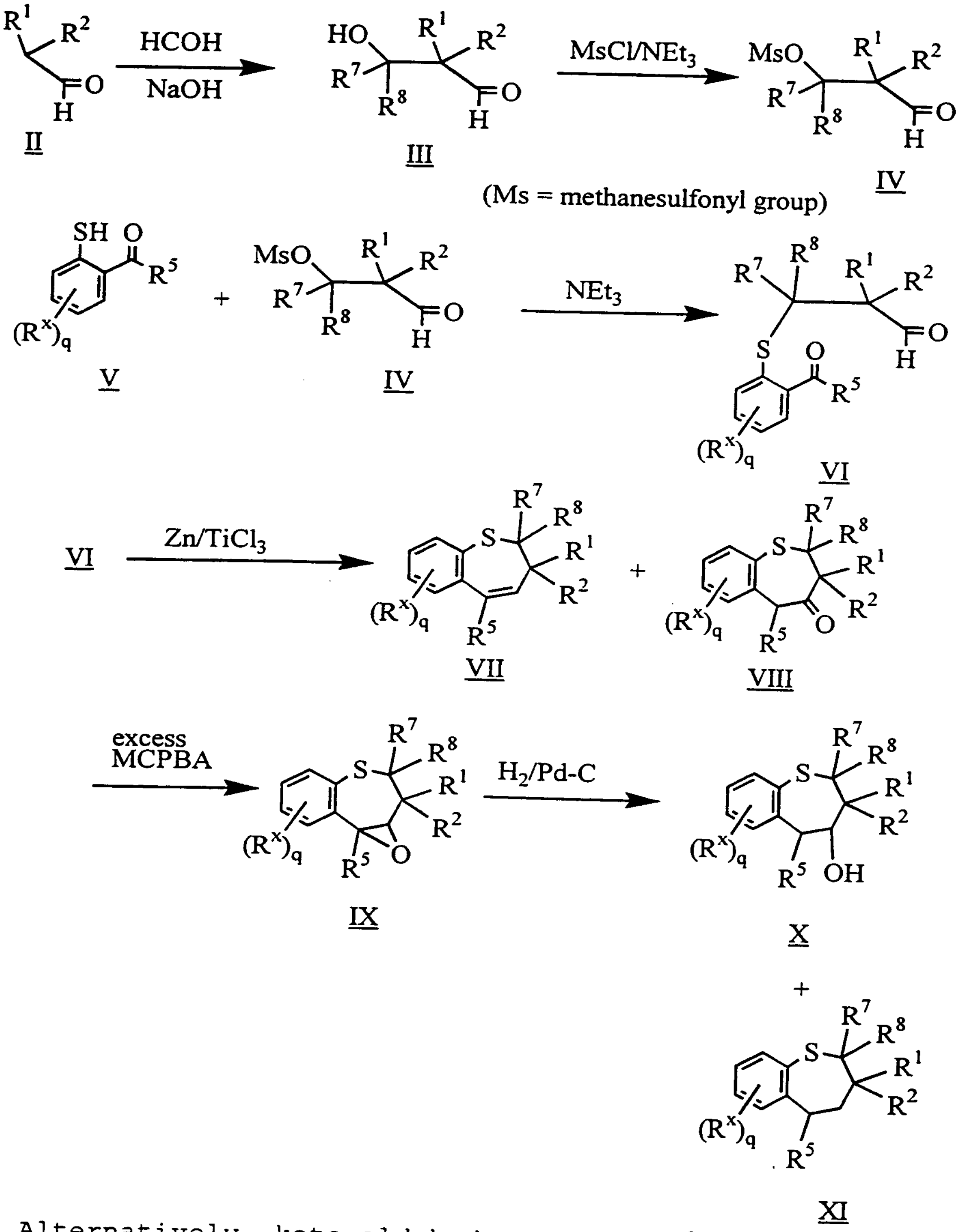
The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

Generally, the compounds of the present invention can be prepared by the procedures described below.

For example, as shown in Scheme I, reaction of aldehyde II with formaldehyde and sodium hydroxide yields the hydroxyaldehyde III which is converted to mesylate IV with methansulfonyl chloride and triethylamine similar to the procedure described in Chem. Ber. **98**, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described in WO 93/16055, in the presence of triethylamine yields keto-aldehyde VI which can be cyclized with the reagent, prepared from zinc and titanium trichloride in refluxing ethylene glycol dimethyl ether (DME), to give a mixture of 2,3-dihydrobenzothiepine VII and two racemic steroisomers of benzothiepin-(5*H*)-4-one VIII when R^1 and R^2 are nonequivalent. Oxidation of VII with 3 equivalents of m-chloro-perbenzoic acid (MCPBA) gives isomeric sulfone-epoxides IX which upon hydrogenation with palladium on carbon as the catalyst yield a mixture of four racemic stereoisomers of 4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X and two racemic stereoisomers of 2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides XI when R^1 and R^2 are nonequivalent.

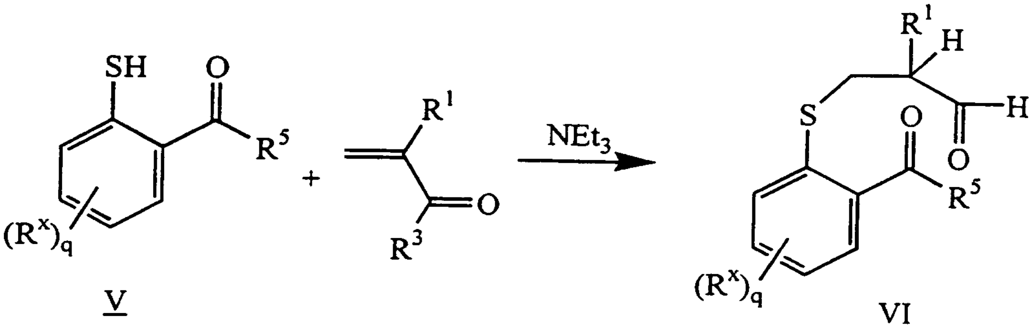
Optically active compounds of the present invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in *J. Org. Chem.*, **39**, 3904 (1974), *ibid.*, **42**, 2781 (1977), and *ibid.*, **44**, 4891 (1979).

Scheme 1


HCOH
NaOH
MsCl/NEt3
(Ms = methanesulfonyl group)
NEt3
Zn/TiCl3
excess MCPBA
H2/Pd-C
II
III
IV
V
IV
VI
VII
VIII
IX
X
XI

Alternatively, keto-aldehyde VI where R^2 is H can be prepared by reaction of thiophenol V with a 2-

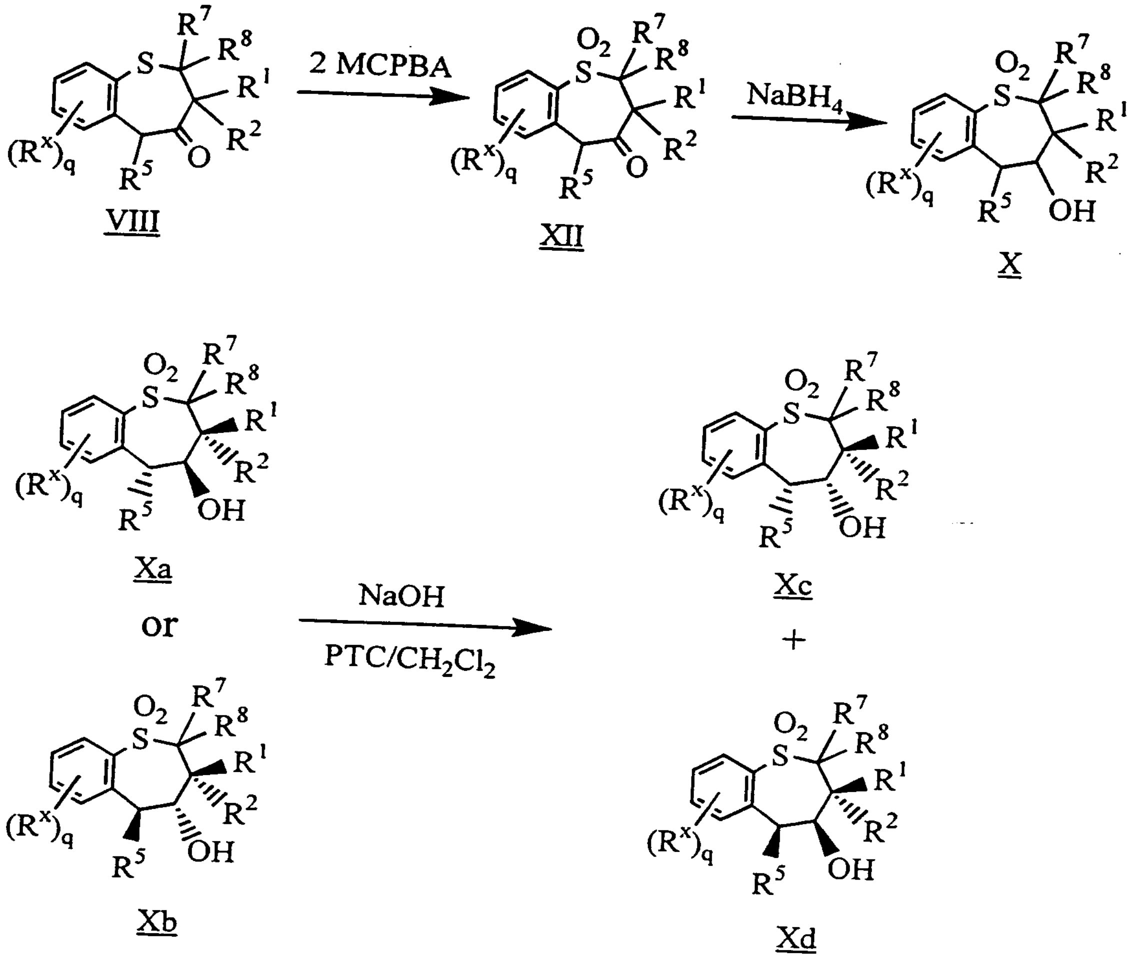
substituted acrolein.



V

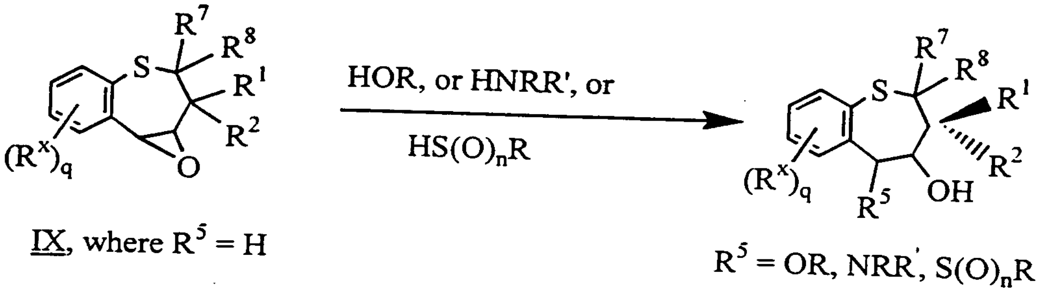
VI

Benzothiepin-(5*H*)-4-one VIII can be oxidized with MCPBA to give the benzothiepin-(5*H*)-4-one-1,1-dioxide XII which can be reduced with sodium borohydride to give four racemic stereoisomers of X. The two stereoisomers of X, Xa and Xb, having the OH group and R^5 on the opposite sides of the benzothiepine ring can be converted to the other two isomers of X, Xc and Xd, having the OH group and R^5 on the same side of the benzothiepine ring by reaction in methylene chloride with 40-50% sodium hydroxide in the presence of a phase transfer catalyst (PTC). The transformation can also be carried out with potassium t-butoxide in THF.


2 MCPBA
NaBH4
VIII
XII
X
Xa
or
Xb
NaOH
PTC/CH2Cl2
Xc
+
Xd

MCPBA = m-chloroperbenzoic acid
PTC = phase transfer catalyst
when R^1= butyl, R^2=ethyl, R^5=phenyl, X=H, q = 4
6a = Xa
6b = Xb
6c = Xc
6d = Xd

The compounds of the present invention where R^5 is OR, NRR′ and $S(O)_nR$ and R^4 is hydroxy can be prepared by reaction of epoxide IX where R^5 is H with thiol, alcohol, and amine in the presence of a base.



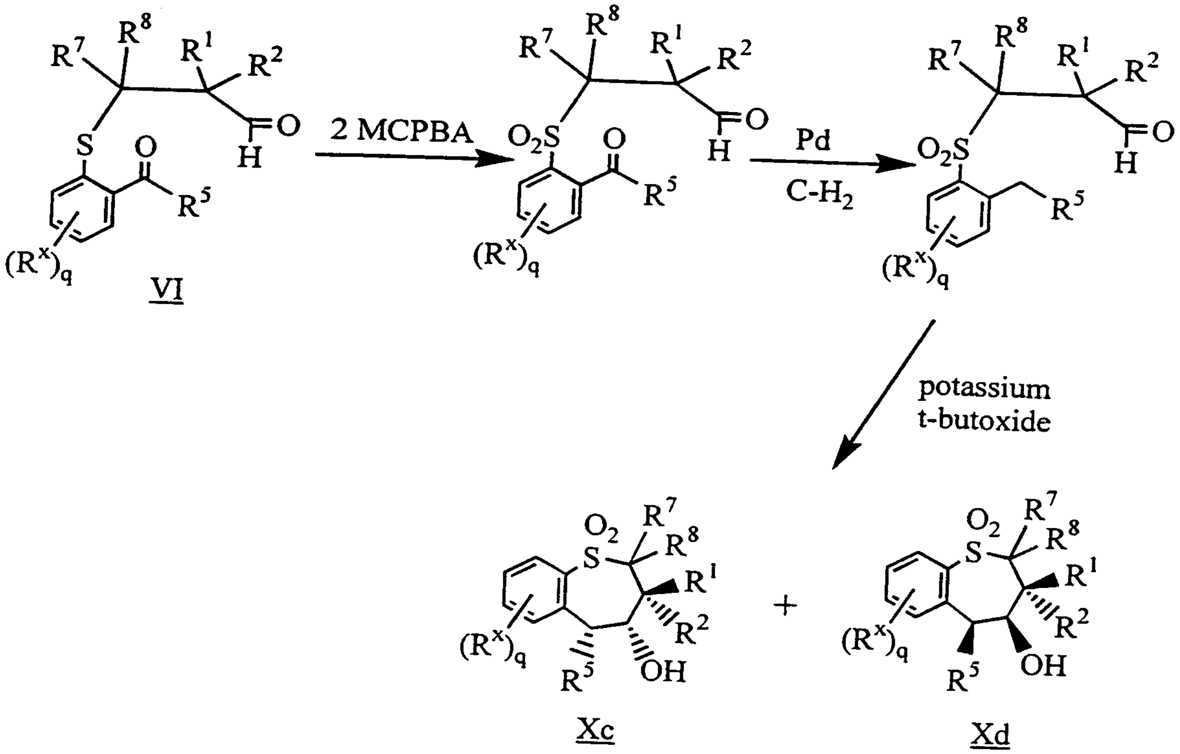
IX, where R^5 = H

R^5 = OR, NRR′, $S(O)_nR$

Another route to Xc and Xd of the present invention is shown in Scheme 2. Compound VI is oxidized to compound XIII with two equivalent of m-chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture of Xc and Xd. Separation of Xc and Xd can be accomplished by either HPLC or fractional crystallization.

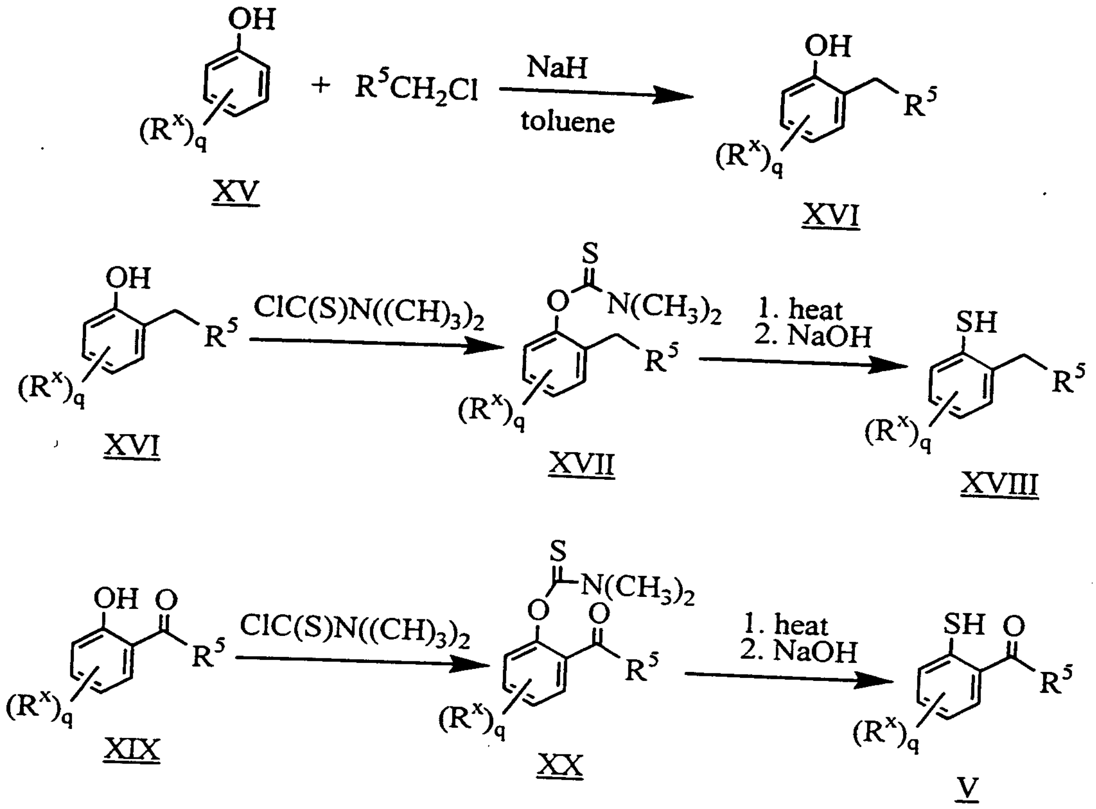
The thiophenols XVIII and V used in the present invention can also be prepared according to the Scheme 3. Alkylation of phenol XV with an arylmethyl chloride in a nonpolar solvent according to the procedure in ***J. Chem. Soc.*, 2431-2432 (1958)** gives the ortho substituted phenol XVI. The phenol XVI can be converted to the thiophenol XVIII via the thiocarbamate XVII by the procedure described in ***J. Org. Chem.*, 31, 3980 (1966)**. The phenol XVI is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give thiocarbamate XVII which is thermally rearranged at 200-300 °C, and the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate thiocarbamate XX.

Scheme 2



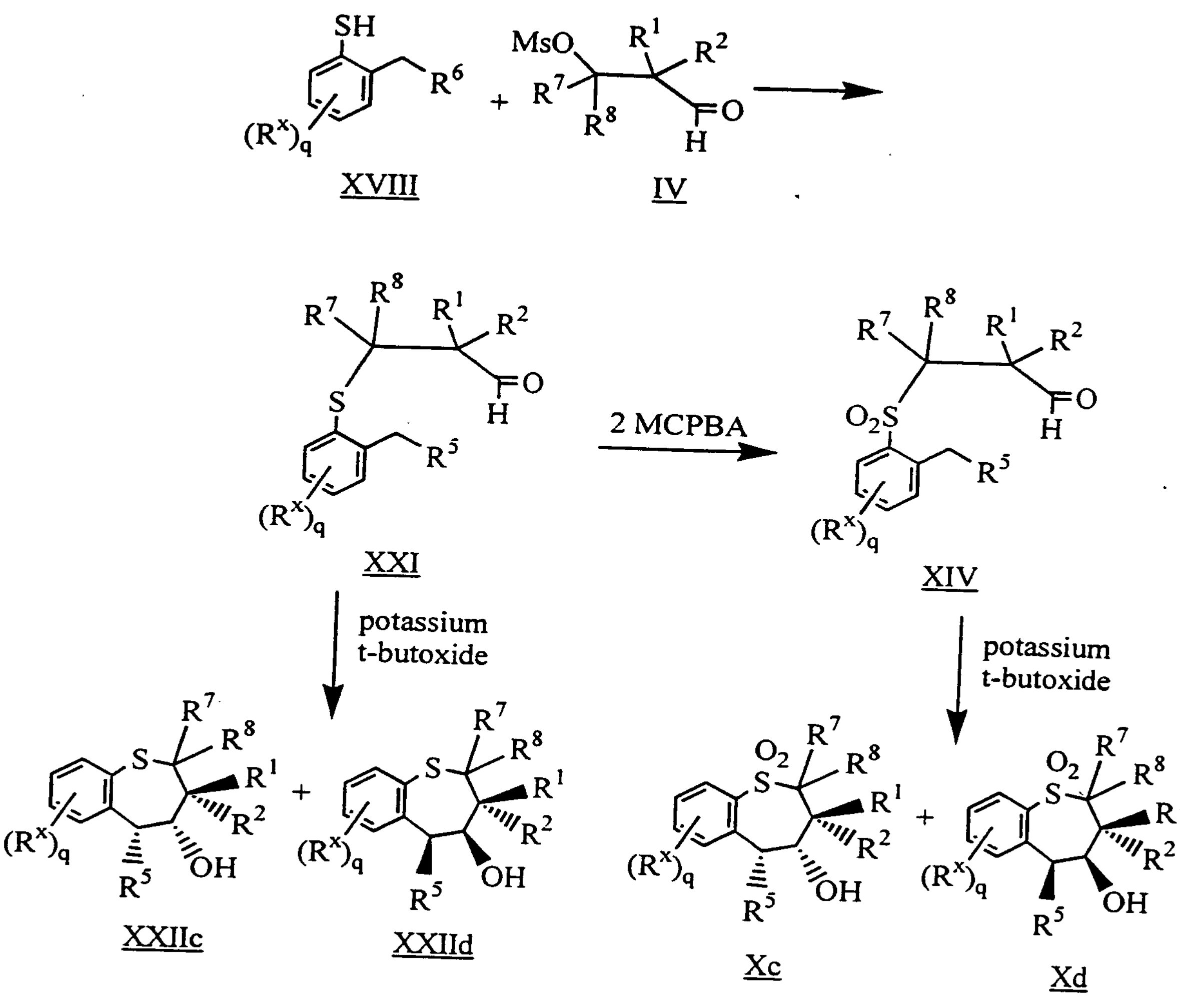
VI
2 MCPBA
Pd
C-H$_2$
potassium
t-butoxide
+
Xc
Xd

Scheme 3


OH
+ R^{5}CH$_2$Cl
NaH
toluene
(R^x)$_q$
R^5
XV
XVI
ClC(S)N((CH)$_3$)$_2$
S
O
N(CH$_3$)$_2$
1. heat
2. NaOH
SH
XVII
XVIII
O
XIX
XX
V

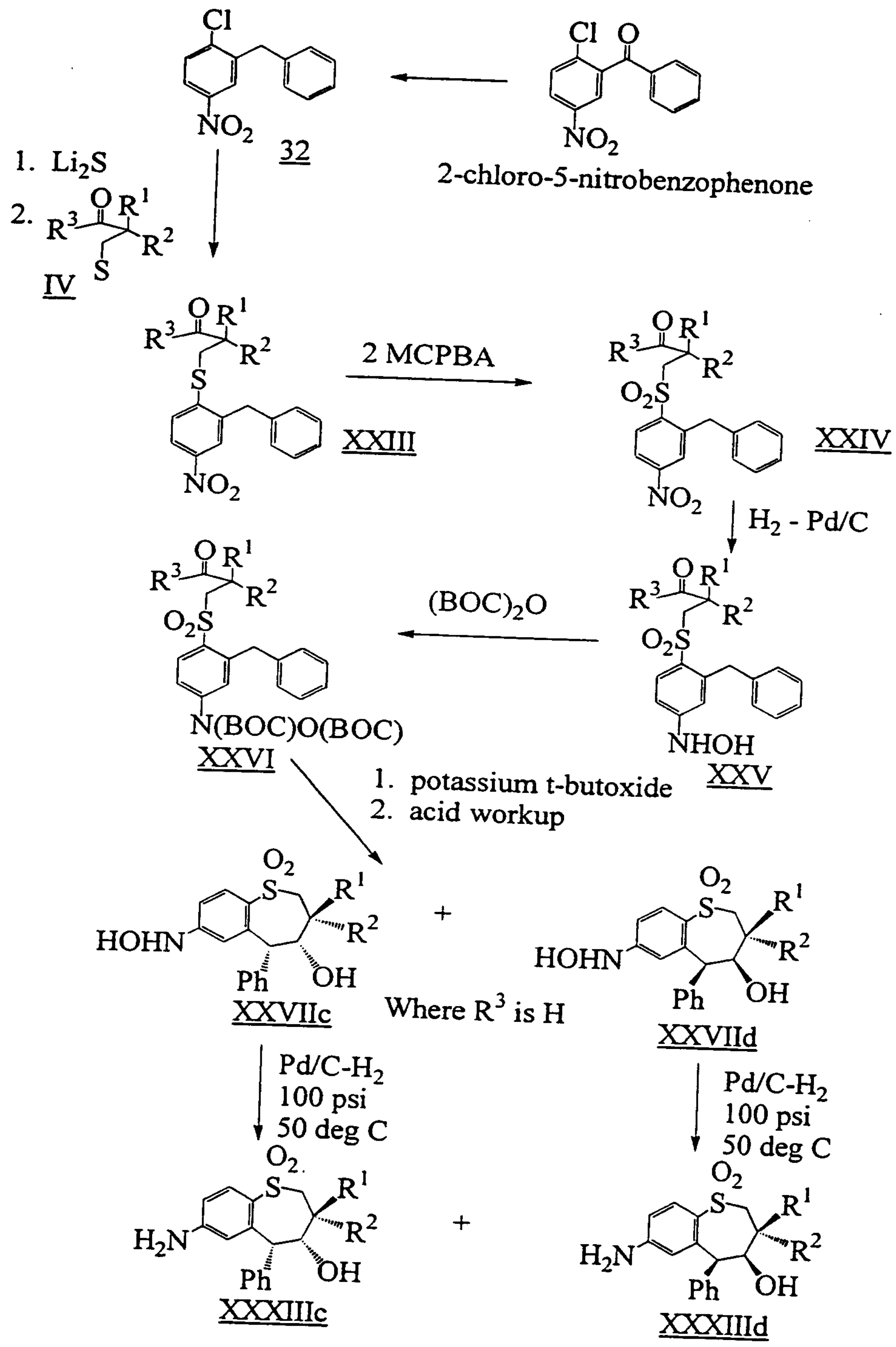
Scheme 4 shows another route to benzothiepine-1,1-dioxides Xc and Xd starting from the thiophenol XVIII. Compound XVIII can be reacted with mesylate IV to give the sulfide-aldehyde XXI. Oxidation of XXI with two equivalents of MCPBA yields the sulfone-aldehyde XIV which can be cyclized with potassium t-butoxide to a mixture of Xc and Xd. Cyclyzation of sulfide-aldehyde with potassium t-butoxide also gives a mixture of benzothiepine XXIIc and XXIId.

Scheme 4


SH
R6
(Rx)q
MsO
R1
R2
R7
R8
O
H
XVIII
IV
R7
R8
R1
R2
S
O
H
R5
(Rx)q
XXI
2 MCPBA
O2S
XIV
potassium
t-butoxide
potassium
t-butoxide
S
OH
XXIIc
XXIId
O2
Xc
Xd

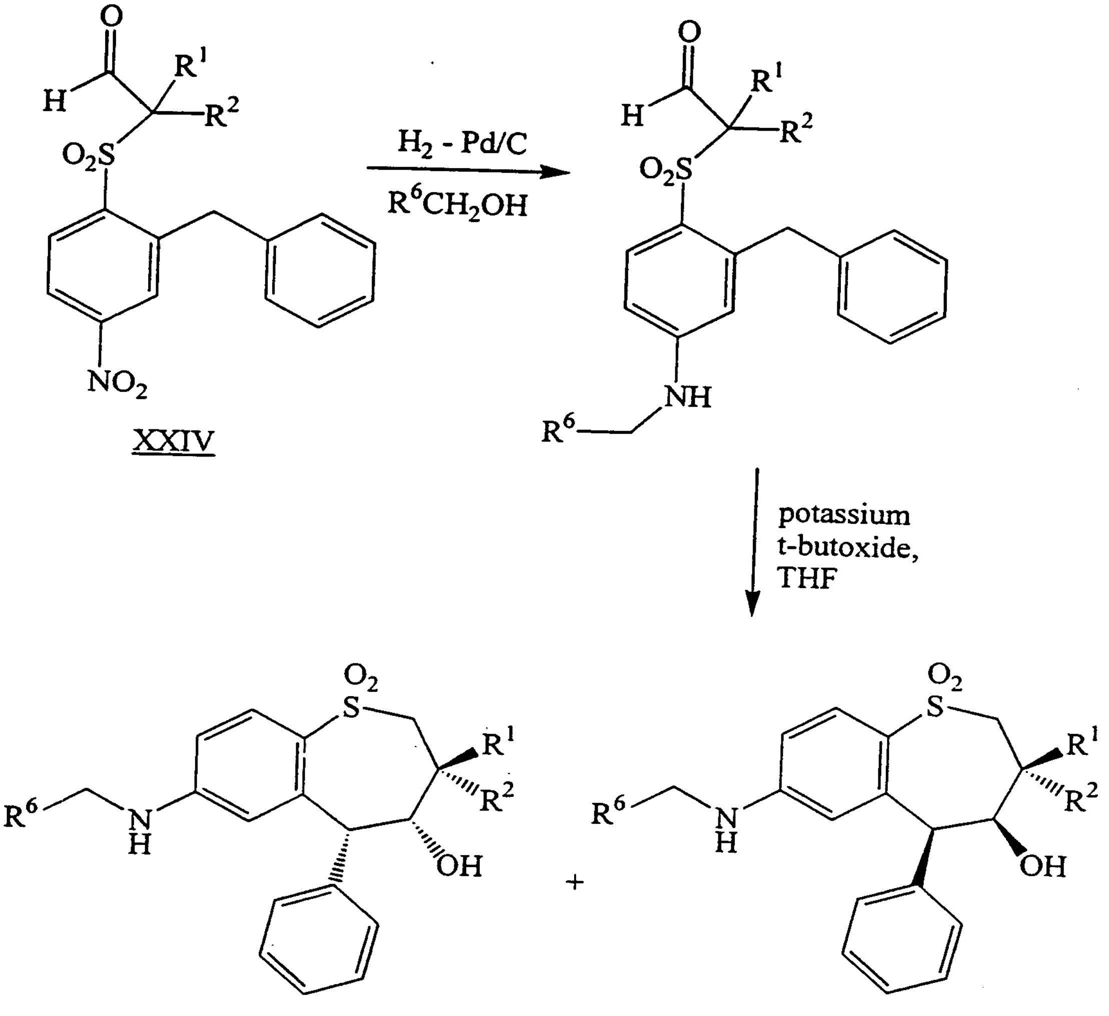
Examples of amine- and hydroxylamine-containing compounds of the present invention can be prepared as shown in Scheme 5 and Scheme 6. 2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane **32**. Reaction of **32** with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV which can be reduced by hydrogenation to the hydroxylamine XXV. Protecting the hydroxylamine XXV with di-t-butyldicarbonate gives the *N,O*-di-(t-butoxycarbonyl)hydroxylamino derivative XXVI. Cyclization of XXVI with potassium t-butoxide and removal of the t-butoxycarbonyl protecting group gives a mixture of hydroxylamino derivatives XXVIIc and XXVIId. The primary amine XXXIIIc and XXXIIId derivatives can also be prepared by further hydrogenation of XXIV or XXVIIc and XXVIId.

Scheme 5


32
2-chloro-5-nitrobenzophenone
1. Li_2S
2.
IV
XXIII
2 MCPBA
XXIV
H_2 - Pd/C
XXV
$(BOC)_2O$
XXVI
N(BOC)O(BOC)
NHOH
1. potassium t-butoxide
2. acid workup
XXVIIc
Where R^3 is H
XXVIId
Pd/C-H_2
100 psi
50 deg C
XXXIIIc
XXXIIId

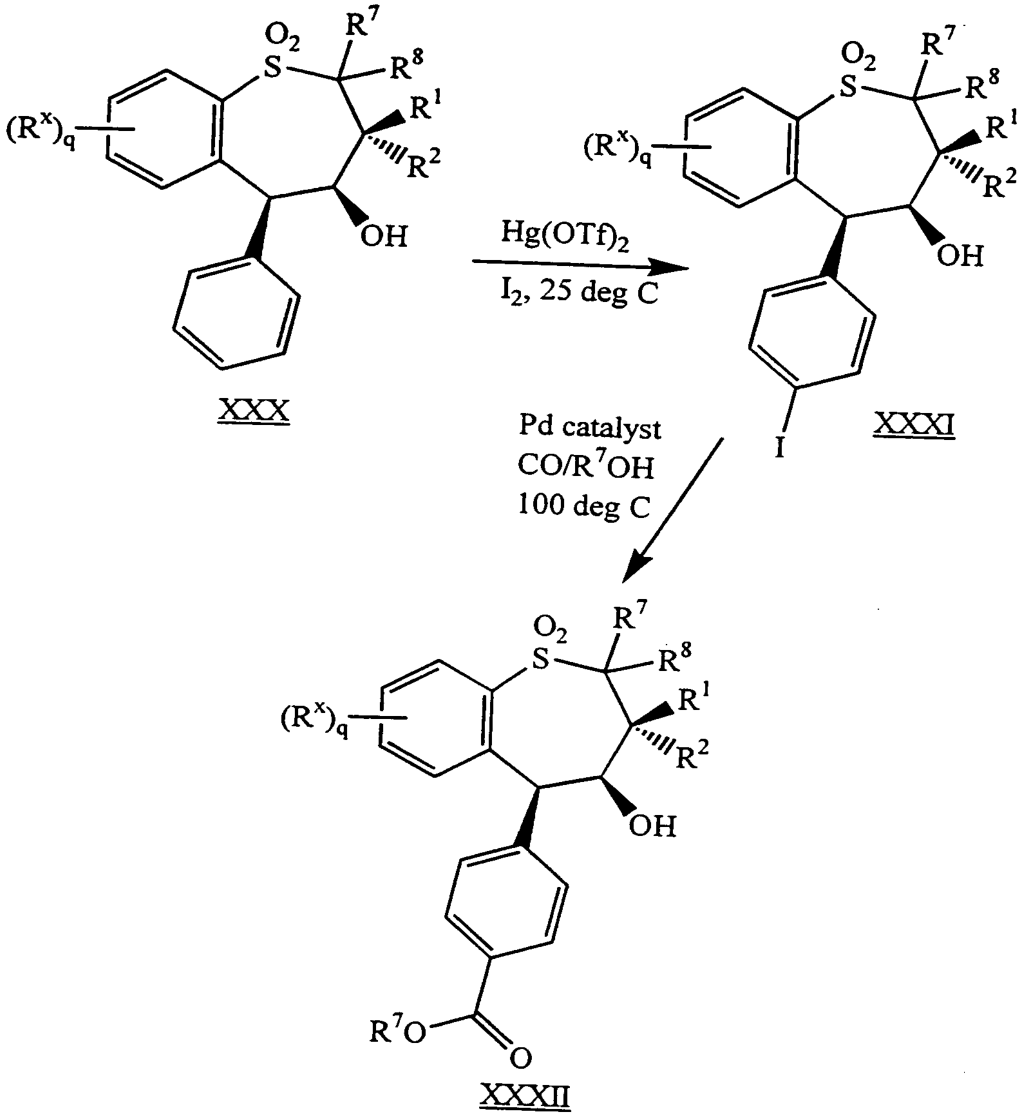
In Scheme 6, reduction of the sulfone-aldehyde XXV with hydrogen followed by reductive alkylation of the resulting amino derivative with hydrogen and an aldehyde catalyzed by palladium on carbon in the same reaction vessel yields the substituted amine derivative XXVIII. Cyclization of XXVIII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention XXIXc and XXIXd.

Scheme 6


XXIV
H_2 - Pd/C
R^6CH_2OH
potassium t-butoxide, THF
XXIXc
XXIXd

Scheme 7 describes one of the methods of introducing a substituent to the aryl ring at the 5-position of benzothiepine. Iodination of 5-phenyl derivative XXX with iodine catalyzed by mercuric triflate gives the iodo derivative XXXI, which upon palladium-catalyzed carbonylation in an alcohol yields the carboxylate XXXII. Hydrolysis of the carboxylate and derivatization of the resulting acid to acid derivatives are well known in the art.

Scheme 7



O2
S
R7
R8
R1
R2
OH
(Rx)q
XXX
Hg(OTf)2
I2, 25 deg C
XXXI
I
Pd catalyst
CO/R7OH
100 deg C
R7O
O
XXXII

Abbreviations used in the foregoing description have the following meanings:

THF---tetrahydrofuran
PTC---phase transfer catalyst
Aliquart 336---methyltricaprylylammonium chloride
MCPBA---m-chloroperbenzoic acid

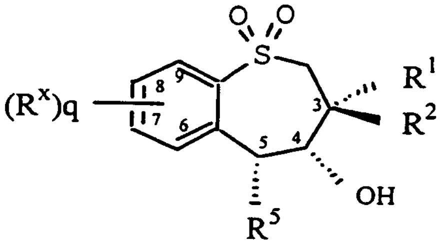
Celite--- a brand of diatomaceous earth filtering aid
DMF---dimethylformamide
DME----ethylene glycol dimethyl ether
BOC---t-butoxycarbonyl group
Me---methyl
Et---ethyl
Bu---butyl
EtOAc---ethyl acetate
Et_2O---diethyl ether
CH_2Cl_2---methylene chloride
$MgSO_4$---magnesium sulfate
NaOH---sodium hydroxide
CH_3OH---methanol
HCl---hydrochloric acid
NaCl---sodium chloride
NaH---sodium hydride
LAH---lithium aluminum hydride
LiOH---lithium hydroxide
Na_2SO_3---sodium sulfite
$NaHCO_3$---sodium bicarbonate
DMSO---dimethylsulfoxide
$KOSiMe_3$---potassium trimethylsilanolate
PEG---polyethylene glycol
MS---mass spectrometry
HRMS---high resolution mass spectrometry
ES---electrospray
NMR---nuclear magnetic resonance spectroscopy
GC---gas chromatography
MPLC---medium pressure liquid chromatography
HPLC---high pressure liquid chromatography
RPHPLC---reverse phase high pressure liquid chromatography
RT---room temperature
h or hr---hour(s)

min---minute(s)

"Enantiomerically-enriched" (e.e.) means that one enantiomer or set of diastereomers preponderates over the complementary enantiomer or set of diastereomers. Enantiomeric enrichment of a mixture of enantiomers is calculated by dividing the concentration of the preponderating enantiomer by the concentration of the other enantiomer, multiplying the dividend by 100, and expressing the result as a percent. Enantiomeric enrichment can be from about 1% to about 100%, preferably from about 10% to about 100%, and more preferably from about 20% to 100%.

R^1 and R^2 can be selected from among substituted and unsubstituted C_1 to C_{10} alkyl wherein the substituent(s) can be selected from among alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing heterocycles joined to the C_1 to C_{10} alkyl through an ether linkage. Substituents at the 3-carbon can include ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, $-CH_2C(=O)C_2H_5$, $-CH_2OC_2H_5$, and $-CH_2O-$(4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl are preferred. In certain particularly preferred compounds of the present invention, substituents R^1 and R^2 are identical, for example n-butyl/n-butyl, so that the compound is achiral at the 3-carbon. Eliminating optical isomerism at the 3-carbon simplifies the selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport inhibitor. In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R^x) on the benzo- ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxy-carbonylalkyl amine, haloalkylthio, haloalkylsulfinyl, haloalkylsufonyl, amino, N-alkylamino, N,N-dialkylamino, (N)-alkoxycarbamoyl, (N)-aryloxycarbamoyl, (N)-aralkyloxycarbamoyl, trialkylammonium (especially with a halide counterion), (N)-amido, (N)-alkylamido, -N-alkylamido, -N,N-dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)-alkylsulfonamido, (N)-haloalkylsulfonamido, carboxyalkyl-amino, trialkylammonium salt, (N)-carbamic acid, alkyl or benzyl ester, N-acylamine, hydroxylamine, haloacylamine, carbohydrate, thiophene a trialkyl ammonium salt having a carboxylic acid or hydroxy substituent on one or more of the alkyl substituents, an alkylene bridge having a quaternary ammonium salt substituted thereon, $-[O(CH_2)_w]_x-X$ where x is 2 to 12, w is 2 or 3 and X is a halo or a quaternary ammonium salt, and (N)-nitrogen containing heterocycle wherein the nitrogen of said heterocycle is optionally quaternized. Among the preferred species which may constitute R^x are methyl, ethyl, isopropyl, t-butyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, bromo, fluoro, methylsulfinyl, methylsulfonyl, ethylthio, amino, hydroxylamine, N-methylamino, N,N-dimethylamino, N,N-diethylamino, (N)-benzyloxycarbamoyl, trimethylammonium, A^-, $-NHC(=O)CH_3$, $-NHC(=O)C_5H_{11}$, $-NHC(=O)C_6H_{13}$, carboxyethylamino, (N)-morpholinyl, (N)-azetidinyl, (N)-N-methylazetidinium A^-, (N)-pyrrolidinyl, pyrrolyl, (N)-N-methylpyridinium A^-, (N)-N-methylmorpholinium A^-, and N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)-N-hexylamino, thiophene, $-N^+(CH_3)_2CO_2H\ I^-$, $-NCH_3CH_2CO_2H$, -(N)-N'-dimethylpiperazinium I^-, (N)-t-butyloxycarbamoyl, (N)-methylsulfonamido, (N)N'-methylpyrrolidinium, and $-(OCH_2CH_2)_3I$, where A^- is a pharmaceutically acceptable anion. The benzo ring is can be mono-substituted at the 6, 7 or 8 position, or disubstituted at the 7- and -8 positions. Also included are the 6,7,8-trialkoxy compounds, for example the 6,7,8-trimethoxy compounds. A variety of other substituents can be advantageously present on the 6, 7, 8, and/or 9- positions of the benzo ring, including, for example, guanidinyl, cycloalkyl, carbohydrate (e.g., a 5 or 6 carbon monosaccharide), peptide, and quaternary ammonium salts linked to the ring via poly(oxyalkylene) linkages, e.g., $-(OCH_2CH_2)_x-N^+R^{13}R^{14}R^{15}A^-$, where x is 2 to 10. Exemplary compounds are those set forth below in Table 1.

Table 1: Alternative Compounds #3 (Family F101.xxx.yyy)



Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)q$
F101.001	01	ethyl	Ph-	7-methyl
	02	ethyl	Ph-	7-ethyl
	03	ethyl	Ph-	7-iso-propyl
	04	ethyl	Ph-	7-tert-butyl
	05	ethyl	Ph-	7-OH
	06	ethyl	Ph-	7-OCH_3
	07	ethyl	Ph-	7-O(iso-propyl)
	08	ethyl	Ph-	7-SCH_3
	09	ethyl	Ph-	7-$SOCH_3$
	10	ethyl	Ph-	7-SO_2CH_3
	11	ethyl	Ph-	7-SCH_2CH_3
	12	ethyl	Ph-	7-NH_2
	13	ethyl	Ph-	7-NHOH
	14	ethyl	Ph-	7-$NHCH_3$
	15	ethyl	Ph-	7-$N(CH_3)_2$
	16	ethyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	ethyl	Ph-	7-$NHC(=O)CH_3$
	18	ethyl	Ph-	7-$N(CH_2CH_3)_2$
	19	ethyl	Ph-	7-$NMeCH_2CO_2H$
	20	ethyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	ethyl	Ph-	7-(N)-morpholine
	22	ethyl	Ph-	7-(N)-azetidine
	23	ethyl	Ph-	7-(N)-N-methylazetidinium, I^-
	24	ethyl	Ph-	7-(N)-pyrrolidine
	25	ethyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	ethyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	ethyl	Ph-	7-(N)-N'-methylpiperazine
	28	ethyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	ethyl	Ph-	7-NH-CBZ
	30	ethyl	Ph-	7-$NHC(O)C_5H_{11}$
	31	ethyl	Ph-	7-$NHC(O)CH_2Br$
	32	ethyl	Ph-	7-$NH-C(NH)NH_2$

33	ethyl	Ph-	7-(2)-thiophene
34	ethyl	Ph-	8-methyl
35	ethyl	Ph-	8-ethyl
36	ethyl	Ph-	8-iso-propyl
37	ethyl	Ph-	8-tert-butyl
38	ethyl	Ph-	8-OH
39	ethyl	Ph-	8-OCH$_3$
40	ethyl	Ph-	8-O(iso-propyl)
41	ethyl	Ph-	8-SCH$_3$
42	ethyl	Ph-	8-SOCH$_3$
43	ethyl	Ph-	8-SO$_2$CH$_3$
44	ethyl	Ph-	8-SCH$_2$CH$_3$
45	ethyl	Ph-	8-NH$_2$
46	ethyl	Ph-	8-NHOH
47	ethyl	Ph-	8-NHCH$_3$
48	ethyl	Ph-	8-N(CH$_3$)$_2$
49	ethyl	Ph-	8-N$^+$(CH$_3$)$_3$, I$^-$
50	ethyl	Ph-	8-NHC(=O)CH$_3$
51	ethyl	Ph-	8-N(CH$_2$CH$_3$)$_2$
52	ethyl	Ph-	8-NMeCH$_2$CO$_2$H
53	ethyl	Ph-	8-N$^+$(Me)$_2$CH$_2$CO$_2$H, I$^-$
54	ethyl	Ph-	8-(N)-morpholine
55	ethyl	Ph-	8-(N)-azetidine
56	ethyl	Ph-	8-(N)-N-methylazetidinium, I$^-$
57	ethyl	Ph-	8-(N)-pyrrolidine
58	ethyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I$^-$
59	ethyl	Ph-	8-(N)-N-methyl-morpholinium, I$^-$
60	ethyl	Ph-	8-(N)-N'-methylpiperazine
61	ethyl	Ph-	8-(N)-N'-dimethylpiperazinium, I$^-$
62	ethyl	Ph-	8-NH-CBZ
63	ethyl	Ph-	8-NHC(O)C$_5$H$_{11}$
64	ethyl	Ph-	8-NHC(O)CH$_2$Br
65	ethyl	Ph-	8-NH-C(NH)NH$_2$
66	ethyl	Ph-	8-(2)-thiophene
67	ethyl	Ph-	9-methyl
68	ethyl	Ph-	9-ethyl
69	ethyl	Ph-	9-iso-propyl
70	ethyl	Ph-	9-tert-butyl
71	ethyl	Ph-	9-OH
72	ethyl	Ph-	9-OCH$_3$
73	ethyl	Ph-	9-O(iso-propyl)
74	ethyl	Ph-	9-SCH$_3$

	75	ethyl	Ph-	9-$SOCH_3$
	76	ethyl	Ph-	9-SO_2CH_3
	77	ethyl	Ph-	9-SCH_2CH_3
	78	ethyl	Ph-	9-NH_2
	79	ethyl	Ph-	9-NHOH
	80	ethyl	Ph-	9-$NHCH_3$
	81	ethyl	Ph-	9-$N(CH_3)_2$
	82	ethyl	Ph-	9-$N^+(CH_3)_3$, I^-
	83	ethyl	Ph-	9-$NHC(=O)CH_3$
	84	ethyl	Ph-	9-$N(CH_2CH_3)_2$
	85	ethyl	Ph-	9-$NMeCH_2CO_2H$
	86	ethyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
	87	ethyl	Ph-	9-(N)-morpholine
	88	ethyl	Ph-	9-(N)-azetidine
	89	ethyl	Ph-	9-(N)-N-methylazetidinium, I^-
	90	ethyl	Ph-	9-(N)-pyrrolidine
	91	ethyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
	92	ethyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
	93	ethyl	Ph-	9-(N)-N'-methylpiperazine
	93	ethyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
	95	ethyl	Ph-	9-NH-CBZ
	96	ethyl	Ph-	9-$NHC(O)C_5H_{11}$
	97	ethyl	Ph-	9-$NHC(O)CH_2Br$
	98	ethyl	Ph-	9-NH-C(NH)NH_2
	99	ethyl	Ph-	9-(2)-thiophene
	100	ethyl	Ph-	7-OCH_3, 8-OCH_3
	101	ethyl	Ph-	7-SCH_3, 8-OCH_3
	102	ethyl	Ph-	7-SCH_3, 8-SCH_3
	103	ethyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.002	01	n-propyl	Ph-	7-methyl
	02	n-propyl	Ph-	7-ethyl
	03	n-propyl	Ph-	7-iso-propyl
	04	n-propyl	Ph-	7-tert-butyl
	05	n-propyl	Ph-	7-OH
	06	n-propyl	Ph-	7-OCH_3
	07	n-propyl	Ph-	7-O(iso-propyl)
	08	n-propyl	Ph-	7-SCH_3
	09	n-propyl	Ph-	7-$SOCH_3$
	10	n-propyl	Ph-	7-SO_2CH_3
	11	n-propyl	Ph-	7-SCH_2CH_3
	12	n-propyl	Ph-	7-NH_2

13	n-propyl	Ph-	7-NHOH
14	n-propyl	Ph-	7-$NHCH_3$
15	n-propyl	Ph-	7-$N(CH_3)_2$
16	n-propyl	Ph-	7-$N^+(CH_3)_3$, I^-
17	n-propyl	Ph-	7-$NHC(=O)CH_3$
18	n-propyl	Ph-	7-$N(CH_2CH_3)_2$
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20	n-propyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	n-propyl	Ph-	7-(N)-morpholine
22	n-propyl	Ph-	7-(N)-azetidine
23	n-propyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	n-propyl	Ph-	7-(N)-pyrrolidine
25	n-propyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	n-propyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	n-propyl	Ph-	7-(N)-N'-methylpiperazine
28	n-propyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	n-propyl	Ph-	7-NH-CBZ
30	n-propyl	Ph-	7-$NHC(O)C_5H_{11}$
31	n-propyl	Ph-	7-$NHC(O)CH_2Br$
32	n-propyl	Ph-	7-$NH-C(NH)NH_2$
33	n-propyl	Ph-	7-(2)-thiophene
34	n-propyl	Ph-	8-methyl
35	n-propyl	Ph-	8-ethyl
36	n-propyl	Ph-	8-iso-propyl
37	n-propyl	Ph-	8-tert-butyl
38	n-propyl	Ph-	8-OH
39	n-propyl	Ph-	8-OCH_3
40	n-propyl	Ph-	8-O(iso-propyl)
41	n-propyl	Ph-	8-SCH_3
42	n-propyl	Ph-	8-$SOCH_3$
43	n-propyl	Ph-	8-SO_2CH_3
44	n-propyl	Ph-	8-SCH_2CH_3
45	n-propyl	Ph-	8-NH_2
46	n-propyl	Ph-	8-NHOH
47	n-propyl	Ph-	8-$NHCH_3$
48	n-propyl	Ph-	8-$N(CH_3)_2$
49	n-propyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-propyl	Ph-	8-$NHC(=O)CH_3$
51	n-propyl	Ph-	8-$N(CH_2CH_3)_2$
52	n-propyl	Ph-	8-$NMeCH_2CO_2H$
53	n-propyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-propyl	Ph-	8-(N)-morpholine

55	n-propyl	Ph-	8-(N)-azetidine
56	n-propyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-propyl	Ph-	8-(N)-pyrrolidine
58	n-propyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-propyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-propyl	Ph-	8-(N)-N′-methylpiperazine
61	n-propyl	Ph-	8-(N)-N′-dimethylpiperazinium, I^-
62	n-propyl	Ph-	8-NH-CBZ
63	n-propyl	Ph-	8-NHC(O)C_5H_{11}
64	n-propyl	Ph-	8-NHC(O)CH_2Br
65	n-propyl	Ph-	8-NH-C(NH)NH_2
66	n-propyl	Ph-	8-(2)-thiophene
67	n-propyl	Ph-	9-methyl
68	n-propyl	Ph-	9-ethyl
69	n-propyl	Ph-	9-iso-propyl
70	n-propyl	Ph-	9-tert-butyl
71	n-propyl	Ph-	9-OH
72	n-propyl	Ph-	9-OCH_3
73	n-propyl	Ph-	9-O(iso-propyl)
74	n-propyl	Ph-	9-SCH_3
75	n-propyl	Ph-	9-$SOCH_3$
76	n-propyl	Ph-	9-SO_2CH_3
77	n-propyl	Ph-	9-SCH_2CH_3
78	n-propyl	Ph-	9-NH_2
79	n-propyl	Ph-	9-NHOH
80	n-propyl	Ph-	9-$NHCH_3$
81	n-propyl	Ph-	9-$N(CH_3)_2$
82	n-propyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	n-propyl	Ph-	9-NHC(=O)CH_3
84	n-propyl	Ph-	9-$N(CH_2CH_3)_2$
85	n-propyl	Ph-	9-$NMeCH_2CO_2H$
86	n-propyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	n-propyl	Ph-	9-(N)-morpholine
88	n-propyl	Ph-	9-(N)-azetidine
89	n-propyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	n-propyl	Ph-	9-(N)-pyrrolidine
91	n-propyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	n-propyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	n-propyl	Ph-	9-(N)-N′-methylpiperazine
93	n-propyl	Ph-	9-(N)-N′-dimethylpiperazinium, I^-
95	n-propyl	Ph-	9-NH-CBZ
96	n-propyl	Ph-	9-NHC(O)C_5H_{11}

	97	n-propyl	Ph-	9-NHC(O)CH_2Br
	98	n-propyl	Ph-	9-NH-C(NH)NH_2
	99	n-propyl	Ph-	9-(2)-thiophene
	100	n-propyl	Ph-	7-OCH_3, 8-OCH_3
	101	n-propyl	Ph-	7-SCH_3, 8-OCH_3
	102	n-propyl	Ph-	7-SCH_3, 8-SCH_3
	103	n-propyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.003	01	n-butyl	Ph-	7-methyl
	02	n-butyl	Ph-	7-ethyl
	03	n-butyl	Ph-	7-iso-propyl
	04	n-butyl	Ph-	7-tert-butyl
	05	n-butyl	Ph-	7-OH
	06	n-butyl	Ph-	7-OCH_3
	07	n-butyl	Ph-	7-O(iso-propyl)
	08	n-butyl	Ph-	7-SCH_3
	09	n-butyl	Ph-	7-$SOCH_3$
	10	n-butyl	Ph-	7-SO_2CH_3
	11	n-butyl	Ph-	7-SCH_2CH_3
	12	n-butyl	Ph-	7-NH_2
	13	n-butyl	Ph-	7-NHOH
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	34	n-butyl	Ph-	8-methyl

35	n-butyl	Ph-	8-ethyl
36	n-butyl	Ph-	8-iso-propyl
37	n-butyl	Ph-	8-tert-butyl
38	n-butyl	Ph-	8-OH
39	n-butyl	Ph-	8-OCH_3
40	n-butyl	Ph-	8-O(iso-propyl)
41	n-butyl	Ph-	8-SCH_3
42	n-butyl	Ph-	8-$SOCH_3$
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70	n-butyl	Ph-	9-tert-butyl
71	n-butyl	Ph-	9-OH
72	n-butyl	Ph-	9-OCH_3
73	n-butyl	Ph-	9-O(iso-propyl)
74	n-butyl	Ph-	9-SCH_3
75	n-butyl	Ph-	9-$SOCH_3$
76	n-butyl	Ph-	9-SO_2CH_3
77	n-butyl	Ph-	9-SCH_2CH_3

	78	n-butyl	Ph-	9-NH_2
	79	n-butyl	Ph-	9-NHOH
	80	n-butyl	Ph-	9-$NHCH_3$
	81	n-butyl	Ph-	9-$N(CH_3)_2$
	82	n-butyl	Ph-	9-$N^+(CH_3)_3$, I^-
	83	n-butyl	Ph-	9-$NHC(=O)CH_3$
	84	n-butyl	Ph-	9-$N(CH_2CH_3)_2$
	85	n-butyl	Ph-	9-$NMeCH_2CO_2H$
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F101.004	01	n-pentyl	Ph-	7-methyl
	02	n-pentyl	Ph-	7-ethyl
	03	n-pentyl	Ph-	7-iso-propyl
	04	n-pentyl	Ph-	7-tert-butyl
	05	n-pentyl	Ph-	7-OH
	06	n-pentyl	Ph-	7-OCH_3
	07	n-pentyl	Ph-	7-O(iso-propyl)
	08	n-pentyl	Ph-	7-SCH_3
	09	n-pentyl	Ph-	7-$SOCH_3$
	10	n-pentyl	Ph-	7-SO_2CH_3
	11	n-pentyl	Ph-	7-SCH_2CH_3
	12	n-pentyl	Ph-	7-NH_2
	13	n-pentyl	Ph-	7-NHOH
	14	n-pentyl	Ph-	7-$NHCH_3$
	15	n-pentyl	Ph-	7-$N(CH_3)_2$

16	n-pentyl	Ph-	7-$N^+(CH_3)_3$, I^-
17	n-pentyl	Ph-	7-$NHC(=O)CH_3$
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31	n-pentyl	Ph-	7-$NHC(O)CH_2Br$
32	n-pentyl	Ph-	7-$NH-C(NH)NH_2$
33	n-pentyl	Ph-	7-(2)-thiophene
34	n-pentyl	Ph-	8-methyl
35	n-pentyl	Ph-	8-ethyl
36	n-pentyl	Ph-	8-iso-propyl
37	n-pentyl	Ph-	8-tert-butyl
38	n-pentyl	Ph-	8-OH
39	n-pentyl	Ph-	8-OCH_3
40	n-pentyl	Ph-	8-O(iso-propyl)
41	n-pentyl	Ph-	8-SCH_3
42	n-pentyl	Ph-	8-$SOCH_3$
43	n-pentyl	Ph-	8-SO_2CH_3
44	n-pentyl	Ph-	8-SCH_2CH_3
45	n-pentyl	Ph-	8-NH_2
46	n-pentyl	Ph-	8-NHOH
47	n-pentyl	Ph-	8-$NHCH_3$
48	n-pentyl	Ph-	8-$N(CH_3)_2$
49	n-pentyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-pentyl	Ph-	8-$NHC(=O)CH_3$
51	n-pentyl	Ph-	8-$N(CH_2CH_3)_2$
52	n-pentyl	Ph-	8-$NMeCH_2CO_2H$
53	n-pentyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-pentyl	Ph-	8-(N)-morpholine
55	n-pentyl	Ph-	8-(N)-azetidine
56	n-pentyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-pentyl	Ph-	8-(N)-pyrrolidine

58	n-pentyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-pentyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-pentyl	Ph-	8-(N)-N'-methylpiperazine
61	n-pentyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	n-pentyl	Ph-	8-NH-CBZ
63	n-pentyl	Ph-	8-NHC(O)C_5H_{11}
64	n-pentyl	Ph-	8-NHC(O)CH_2Br
65	n-pentyl	Ph-	8-NH-C(NH)NH_2
66	n-pentyl	Ph-	8-(2)-thiophene
67	n-pentyl	Ph-	9-methyl
68	n-pentyl	Ph-	9-ethyl
69	n-pentyl	Ph-	9-iso-propyl
70	n-pentyl	Ph-	9-tert-butyl
71	n-pentyl	Ph-	9-OH
72	n-pentyl	Ph-	9-OCH_3
73	n-pentyl	Ph-	9-O(iso-propyl)
74	n-pentyl	Ph-	9-SCH_3
75	n-pentyl	Ph-	9-$SOCH_3$
76	n-pentyl	Ph-	9-SO_2CH_3
77	n-pentyl	Ph-	9-SCH_2CH_3
78	n-pentyl	Ph-	9-NH_2
79	n-pentyl	Ph-	9-NHOH
80	n-pentyl	Ph-	9-$NHCH_3$
81	n-pentyl	Ph-	9-$N(CH_3)_2$
82	n-pentyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	n-pentyl	Ph-	9-NHC(=O)CH_3
84	n-pentyl	Ph-	9-$N(CH_2CH_3)_2$
85	n-pentyl	Ph-	9-$NMeCH_2CO_2H$
86	n-pentyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	n-pentyl	Ph-	9-(N)-morpholine
88	n-pentyl	Ph-	9-(N)-azetidine
89	n-pentyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	n-pentyl	Ph-	9-(N)-pyrrolidine
91	n-pentyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	n-pentyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	n-pentyl	Ph-	9-(N)-N'-methylpiperazine
93	n-pentyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	n-pentyl	Ph-	9-NH-CBZ
96	n-pentyl	Ph-	9-NHC(O)C_5H_{11}
97	n-pentyl	Ph-	9-NHC(O)CH_2Br
98	n-pentyl	Ph-	9-NH-C(NH)NH_2
99	n-pentyl	Ph-	9-(2)-thiophene

	100	n-pentyl	Ph-	7-OCH_3, 8-OCH_3
	101	n-pentyl	Ph-	7-SCH_3, 8-OCH_3
	102	n-pentyl	Ph-	7-SCH_3, 8-SCH_3
	103	n-pentyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.005	01	n-hexyl	Ph-	7-methyl
	02	n-hexyl	Ph-	7-ethyl
	03	n-hexyl	Ph-	7-iso-propyl
	04	n-hexyl	Ph-	7-tert-butyl
	05	n-hexyl	Ph-	7-OH
	06	n-hexyl	Ph-	7-OCH_3
	07	n-hexyl	Ph-	7-O(iso-propyl)
	08	n-hexyl	Ph-	7-SCH_3
	09	n-hexyl	Ph-	7-$SOCH_3$
	10	n-hexyl	Ph-	7-SO_2CH_3
	11	n-hexyl	Ph-	7-SCH_2CH_3
	12	n-hexyl	Ph-	7-NH_2
	13	n-hexyl	Ph-	7-NHOH
	14	n-hexyl	Ph-	7-$NHCH_3$
	15	n-hexyl	Ph-	7-$N(CH_3)_2$
	16	n-hexyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	n-hexyl	Ph-	7-$NHC(=O)CH_3$
	18	n-hexyl	Ph-	7-$N(CH_2CH_3)_2$
	19	n-hexyl	Ph-	7-$NMeCH_2CO_2H$
	20	n-hexyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	n-hexyl	Ph-	7-(N)-morpholine
	22	n-hexyl	Ph-	7-(N)-azetidine
	23	n-hexyl	Ph-	7-(N)-N-methylazetidinium, I^-
	24	n-hexyl	Ph-	7-(N)-pyrrolidine
	25	n-hexyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	n-hexyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	n-hexyl	Ph-	7-(N)-N′-methylpiperazine
	28	n-hexyl	Ph-	7-(N)-N′-dimethylpiperazinium, I^-
	29	n-hexyl	Ph-	7-NH-CBZ
	30	n-hexyl	Ph-	7-$NHC(O)C_5H_{11}$
	31	n-hexyl	Ph-	7-$NHC(O)CH_2Br$
	32	n-hexyl	Ph-	7-$NH-C(NH)NH_2$
	33	n-hexyl	Ph-	7-(2)-thiophene
	34	n-hexyl	Ph-	8-methyl
	35	n-hexyl	Ph-	8-ethyl
	36	n-hexyl	Ph-	8-iso-propyl
	37	n-hexyl	Ph-	8-tert-butyl

38	n-hexyl	Ph-	8-OH
39	n-hexyl	Ph-	8-OCH_3
40	n-hexyl	Ph-	8-O(iso-propyl)
41	n-hexyl	Ph-	8-SCH_3
42	n-hexyl	Ph-	8-$SOCH_3$
43	n-hexyl	Ph-	8-SO_2CH_3
44	n-hexyl	Ph-	8-SCH_2CH_3
45	n-hexyl	Ph-	8-NH_2
46	n-hexyl	Ph-	8-NHOH
47	n-hexyl	Ph-	8-$NHCH_3$
48	n-hexyl	Ph-	8-$N(CH_3)_2$
49	n-hexyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-hexyl	Ph-	8-$NHC(=O)CH_3$
51	n-hexyl	Ph-	8-$N(CH_2CH_3)_2$
52	n-hexyl	Ph-	8-$NMeCH_2CO_2H$
53	n-hexyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-hexyl	Ph-	8-(N)-morpholine
55	n-hexyl	Ph-	8-(N)-azetidine
56	n-hexyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-hexyl	Ph-	8-(N)-pyrrolidine
58	n-hexyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-hexyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-hexyl	Ph-	8-(N)-N′-methylpiperazine
61	n-hexyl	Ph-	8-(N)-N′-dimethylpiperazinium, I^-
62	n-hexyl	Ph-	8-NH-CBZ
63	n-hexyl	Ph-	8-$NHC(O)C_5H_{11}$
64	n-hexyl	Ph-	8-$NHC(O)CH_2Br$
65	n-hexyl	Ph-	8-$NH-C(NH)NH_2$
66	n-hexyl	Ph-	8-(2)-thiophene
67	n-hexyl	Ph-	9-methyl
68	n-hexyl	Ph-	9-ethyl
69	n-hexyl	Ph-	9-iso-propyl
70	n-hexyl	Ph-	9-tert-butyl
71	n-hexyl	Ph-	9-OH
72	n-hexyl	Ph-	9-OCH_3
73	n-hexyl	Ph-	9-O(iso-propyl)
74	n-hexyl	Ph-	9-SCH_3
75	n-hexyl	Ph-	9-$SOCH_3$
76	n-hexyl	Ph-	9-SO_2CH_3
77	n-hexyl	Ph-	9-SCH_2CH_3
78	n-hexyl	Ph-	9-NH_2
79	n-hexyl	Ph-	9-NHOH

	80	n-hexyl	Ph-	9-$NHCH_3$
	81	n-hexyl	Ph-	9-$N(CH_3)_2$
	82	n-hexyl	Ph-	9-$N^+(CH_3)_3$, I^-
	83	n-hexyl	Ph-	9-$NHC(=O)CH_3$
	84	n-hexyl	Ph-	9-$N(CH_2CH_3)_2$
	85	n-hexyl	Ph-	9-$NMeCH_2CO_2H$
	86	n-hexyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
	87	n-hexyl	Ph-	9-(N)-morpholine
	88	n-hexyl	Ph-	9-(N)-azetidine
	89	n-hexyl	Ph-	9-(N)-N-methylazetidinium, I^-
	90	n-hexyl	Ph-	9-(N)-pyrrolidine
	91	n-hexyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
	92	n-hexyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
	93	n-hexyl	Ph-	9-(N)-N'-methylpiperazine
	93	n-hexyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
	95	n-hexyl	Ph-	9-NH-CBZ
	96	n-hexyl	Ph-	9-$NHC(O)C_5H_{11}$
	97	n-hexyl	Ph-	9-$NHC(O)CH_2Br$
	98	n-hexyl	Ph-	9-$NH-C(NH)NH_2$
	99	n-hexyl	Ph-	9-(2)-thiophene
	100	n-hexyl	Ph-	7-OCH_3, 8-OCH_3
	101	n-hexyl	Ph-	7-SCH_3, 8-OCH_3
	102	n-hexyl	Ph-	7-SCH_3, 8-SCH_3
	103	n-hexyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.006	01	iso-propyl	Ph-	7-methyl
	02	iso-propyl	Ph-	7-ethyl
	03	iso-propyl	Ph-	7-iso-propyl
	04	iso-propyl	Ph-	7-tert-butyl
	05	iso-propyl	Ph-	7-OH
	06	iso-propyl	Ph-	7-OCH_3
	07	iso-propyl	Ph-	7-O(iso-propyl)
	08	iso-propyl	Ph-	7-SCH_3
	09	iso-propyl	Ph-	7-$SOCH_3$
	10	iso-propyl	Ph-	7-SO_2CH_3
	11	iso-propyl	Ph-	7-SCH_2CH_3
	12	iso-propyl	Ph-	7-NH_2
	13	iso-propyl	Ph-	7-NHOH
	14	iso-propyl	Ph-	7-$NHCH_3$
	15	iso-propyl	Ph-	7-$N(CH_3)_2$
	16	iso-propyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	iso-propyl	Ph-	7-$NHC(=O)CH_3$

18	iso-propyl	Ph-	7-N$(CH_2CH_3)_2$
19	iso-propyl	Ph-	7-NMeCH_2CO_2H
20	iso-propyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	iso-propyl	Ph-	7-(N)-morpholine
22	iso-propyl	Ph-	7-(N)-azetidine
23	iso-propyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	iso-propyl	Ph-	7-(N)-pyrrolidine
25	iso-propyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	iso-propyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	iso-propyl	Ph-	7-(N)-N′-methylpiperazine
28	iso-propyl	Ph-	7-(N)-N′-dimethylpiperazinium, I^-
29	iso-propyl	Ph-	7-NH-CBZ
30	iso-propyl	Ph-	7-NHC(O)C_5H_{11}
31	iso-propyl	Ph-	7-NHC(O)CH_2Br
32	iso-propyl	Ph-	7-NH-C(NH)NH_2
33	iso-propyl	Ph-	7-(2)-thiophene
34	iso-propyl	Ph-	8-methyl
35	iso-propyl	Ph-	8-ethyl
36	iso-propyl	Ph-	8-iso-propyl
37	iso-propyl	Ph-	8-tert-butyl
38	iso-propyl	Ph-	8-OH
39	iso-propyl	Ph-	8-OCH_3
40	iso-propyl	Ph-	8-O(iso-propyl)
41	iso-propyl	Ph-	8-SCH_3
42	iso-propyl	Ph-	8-$SOCH_3$
43	iso-propyl	Ph-	8-SO_2CH_3
44	iso-propyl	Ph-	8-SCH_2CH_3
45	iso-propyl	Ph-	8-NH_2
46	iso-propyl	Ph-	8-NHOH
47	iso-propyl	Ph-	8-$NHCH_3$
48	iso-propyl	Ph-	8-N$(CH_3)_2$
49	iso-propyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	iso-propyl	Ph-	8-NHC(=O)CH_3
51	iso-propyl	Ph-	8-N$(CH_2CH_3)_2$
52	iso-propyl	Ph-	8-NMeCH_2CO_2H
53	iso-propyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	iso-propyl	Ph-	8-(N)-morpholine
55	iso-propyl	Ph-	8-(N)-azetidine
56	iso-propyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	iso-propyl	Ph-	8-(N)-pyrrolidine
58	iso-propyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	iso-propyl	Ph-	8-(N)-N-methyl-morpholinium, I^-

60	iso-propyl	Ph-	8-(N)-N'-methylpiperazine
61	iso-propyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	iso-propyl	Ph-	8-NH-CBZ
63	iso-propyl	Ph-	8-NHC(O)C_5H_{11}
64	iso-propyl	Ph-	8-NHC(O)CH_2Br
65	iso-propyl	Ph-	8-NH-C(NH)NH_2
66	iso-propyl	Ph-	8-(2)-thiophene
67	iso-propyl	Ph-	9-methyl
68	iso-propyl	Ph-	9-ethyl
69	iso-propyl	Ph-	9-iso-propyl
70	iso-propyl	Ph-	9-tert-butyl
71	iso-propyl	Ph-	9-OH
72	iso-propyl	Ph-	9-OCH_3
73	iso-propyl	Ph-	9-O(iso-propyl)
74	iso-propyl	Ph-	9-SCH_3
75	iso-propyl	Ph-	9-$SOCH_3$
76	iso-propyl	Ph-	9-SO_2CH_3
77	iso-propyl	Ph-	9-SCH_2CH_3
78	iso-propyl	Ph-	9-NH_2
79	iso-propyl	Ph-	9-NHOH
80	iso-propyl	Ph-	9-$NHCH_3$
81	iso-propyl	Ph-	9-$N(CH_3)_2$
82	iso-propyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	iso-propyl	Ph-	9-NHC(=O)CH_3
84	iso-propyl	Ph-	9-$N(CH_2CH_3)_2$
85	iso-propyl	Ph-	9-$NMeCH_2CO_2H$
86	iso-propyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	iso-propyl	Ph-	9-(N)-morpholine
88	iso-propyl	Ph-	9-(N)-azetidine
89	iso-propyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	iso-propyl	Ph-	9-(N)-pyrrolidine
91	iso-propyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	iso-propyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	iso-propyl	Ph-	9-(N)-N'-methylpiperazine
93	iso-propyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	iso-propyl	Ph-	9-NH-CBZ
96	iso-propyl	Ph-	9-NHC(O)C_5H_{11}
97	iso-propyl	Ph-	9-NHC(O)CH_2Br
98	iso-propyl	Ph-	9-NH-C(NH)NH_2
99	iso-propyl	Ph-	9-(2)-thiophene
100	iso-propyl	Ph-	7-OCH_3, 8-OCH_3

	101	iso-propyl	Ph-	7-SCH_3, 8-OCH_3
	102	iso-propyl	Ph-	7-SCH_3, 8-SCH_3
	103	iso-propyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.007	01	iso-butyl	Ph-	7-methyl
	02	iso-butyl	Ph-	7-ethyl
	03	iso-butyl	Ph-	7-iso-propyl
	04	iso-butyl	Ph-	7-tert-butyl
	05	iso-butyl	Ph-	7-OH
	06	iso-butyl	Ph-	7-OCH_3
	07	iso-butyl	Ph-	7-O(iso-propyl)
	08	iso-butyl	Ph-	7-SCH_3
	09	iso-butyl	Ph-	7-$SOCH_3$
	10	iso-butyl	Ph-	7-SO_2CH_3
	11	iso-butyl	Ph-	7-SCH_2CH_3
	12	iso-butyl	Ph-	7-NH_2
	13	iso-butyl	Ph-	7-NHOH
	14	iso-butyl	Ph-	7-$NHCH_3$
	15	iso-butyl	Ph-	7-$N(CH_3)_2$
	16	iso-butyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	iso-butyl	Ph-	7-NHC(=O)CH_3
	18	iso-butyl	Ph-	7-$N(CH_2CH_3)_2$
	19	iso-butyl	Ph-	7-$NMeCH_2CO_2H$
	20	iso-butyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	iso-butyl	Ph-	7-(N)-morpholine
	22	iso-butyl	Ph-	7-(N)-azetidine
	23	iso-butyl	Ph-	7-(N)-N-methylazetidinium, I^-
	24	iso-butyl	Ph-	7-(N)-pyrrolidine
	25	iso-butyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	iso-butyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	iso-butyl	Ph-	7-(N)-N'-methylpiperazine
	28	iso-butyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	iso-butyl	Ph-	7-NH-CBZ
	30	iso-butyl	Ph-	7-NHC(O)C_5H_{11}
	31	iso-butyl	Ph-	7-NHC(O)CH_2Br
	32	iso-butyl	Ph-	7-NH-C(NH)NH_2
	33	iso-butyl	Ph-	7-(2)-thiophene
	34	iso-butyl	Ph-	8-methyl
	35	iso-butyl	Ph-	8-ethyl
	36	iso-butyl	Ph-	8-iso-propyl
	37	iso-butyl	Ph-	8-tert-butyl
	38	iso-butyl	Ph-	8-OH
	39	iso-butyl	Ph-	8-OCH_3

40	iso-butyl	Ph-	8-O(iso-propyl)
41	iso-butyl	Ph-	8-SCH_3
42	iso-butyl	Ph-	8-$SOCH_3$
43	iso-butyl	Ph-	8-SO_2CH_3
44	iso-butyl	Ph-	8-SCH_2CH_3
45	iso-butyl	Ph-	8-NH_2
46	iso-butyl	Ph-	8-NHOH
47	iso-butyl	Ph-	8-$NHCH_3$
48	iso-butyl	Ph-	8-$N(CH_3)_2$
49	iso-butyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	iso-butyl	Ph-	8-$NHC(=O)CH_3$
51	iso-butyl	Ph-	8-$N(CH_2CH_3)_2$
52	iso-butyl	Ph-	8-$NMeCH_2CO_2H$
53	iso-butyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	iso-butyl	Ph-	8-(N)-morpholine
55	iso-butyl	Ph-	8-(N)-azetidine
56	iso-butyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	iso-butyl	Ph-	8-(N)-pyrrolidine
58	iso-butyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	iso-butyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	iso-butyl	Ph-	8-(N)-N'-methylpiperazine
61	iso-butyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	iso-butyl	Ph-	8-NH-CBZ
63	iso-butyl	Ph-	8-$NHC(O)C_5H_{11}$
64	iso-butyl	Ph-	8-$NHC(O)CH_2Br$
65	iso-butyl	Ph-	8-$NH-C(NH)NH_2$
66	iso-butyl	Ph-	8-(2)-thiophene
67	iso-butyl	Ph-	9-methyl
68	iso-butyl	Ph-	9-ethyl
69	iso-butyl	Ph-	9-iso-propyl
70	iso-butyl	Ph-	9-tert-butyl
71	iso-butyl	Ph-	9-OH
72	iso-butyl	Ph-	9-OCH_3
73	iso-butyl	Ph-	9-O(iso-propyl)
74	iso-butyl	Ph-	9-SCH_3
75	iso-butyl	Ph-	9-$SOCH_3$
76	iso-butyl	Ph-	9-SO_2CH_3
77	iso-butyl	Ph-	9-SCH_2CH_3
78	iso-butyl	Ph-	9-NH_2
79	iso-butyl	Ph-	9-NHOH
80	iso-butyl	Ph-	9-$NHCH_3$
81	iso-butyl	Ph-	9-$N(CH_3)_2$

	82	iso-butyl	Ph-	9-$N^+(CH_3)_3$, I^-
	83	iso-butyl	Ph-	9-$NHC(=O)CH_3$
	84	iso-butyl	Ph-	9-$N(CH_2CH_3)_2$
	85	iso-butyl	Ph-	9-$NMeCH_2CO_2H$
	86	iso-butyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
	87	iso-butyl	Ph-	9-(N)-morpholine
	88	iso-butyl	Ph-	9-(N)-azetidine
	89	iso-butyl	Ph-	9-(N)-N-methylazetidinium, I^-
	90	iso-butyl	Ph-	9-(N)-pyrrolidine
	91	iso-butyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
	92	iso-butyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
	93	iso-butyl	Ph-	9-(N)-N'-methylpiperazine
	93	iso-butyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
	95	iso-butyl	Ph-	9-NH-CBZ
	96	iso-butyl	Ph-	9-$NHC(O)C_5H_{11}$
	97	iso-butyl	Ph-	9-$NHC(O)CH_2Br$
	98	iso-butyl	Ph-	9-$NH\text{-}C(NH)NH_2$
	99	iso-butyl	Ph-	9-(2)-thiophene
	100	iso-butyl	Ph-	7-OCH_3, 8-OCH_3
	101	iso-butyl	Ph-	7-SCH_3, 8-OCH_3
	102	iso-butyl	Ph-	7-SCH_3, 8-SCH_3
	103	iso-butyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.008	01	iso-pentyl	Ph-	7-methyl
	02	iso-pentyl	Ph-	7-ethyl
	03	iso-pentyl	Ph-	7-iso-propyl
	04	iso-pentyl	Ph-	7-tert-butyl
	05	iso-pentyl	Ph-	7-OH
	06	iso-pentyl	Ph-	7-OCH_3
	07	iso-pentyl	Ph-	7-O(iso-propyl)
	08	iso-pentyl	Ph-	7-SCH_3
	09	iso-pentyl	Ph-	7-$SOCH_3$
	10	iso-pentyl	Ph-	7-SO_2CH_3
	11	iso-pentyl	Ph-	7-SCH_2CH_3
	12	iso-pentyl	Ph-	7-NH_2
	13	iso-pentyl	Ph-	7-NHOH
	14	iso-pentyl	Ph-	7-$NHCH_3$
	15	iso-pentyl	Ph-	7-$N(CH_3)_2$
	16	iso-pentyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	iso-pentyl	Ph-	7-$NHC(=O)CH_3$
	18	iso-pentyl	Ph-	7-$N(CH_2CH_3)_2$
	19	iso-pentyl	Ph-	7-$NMeCH_2CO_2H$

20	iso-pentyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	iso-pentyl	Ph-	7-(N)-morpholine
22	iso-pentyl	Ph-	7-(N)-azetidine
23	iso-pentyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	iso-pentyl	Ph-	7-(N)-pyrrolidine
25	iso-pentyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	iso-pentyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	iso-pentyl	Ph-	7-(N)-N'-methylpiperazine
28	iso-pentyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	iso-pentyl	Ph-	7-NH-CBZ
30	iso-pentyl	Ph-	7-$NHC(O)C_5H_{11}$
31	iso-pentyl	Ph-	7-$NHC(O)CH_2Br$
32	iso-pentyl	Ph-	7-$NH-C(NH)NH_2$
33	iso-pentyl	Ph-	7-(2)-thiophene
34	iso-pentyl	Ph-	8-methyl
35	iso-pentyl	Ph-	8-ethyl
36	iso-pentyl	Ph-	8-iso-propyl
37	iso-pentyl	Ph-	8-tert-butyl
38	iso-pentyl	Ph-	8-OH
39	iso-pentyl	Ph-	8-OCH_3
40	iso-pentyl	Ph-	8-O(iso-propyl)
41	iso-pentyl	Ph-	8-SCH_3
42	iso-pentyl	Ph-	8-$SOCH_3$
43	iso-pentyl	Ph-	8-SO_2CH_3
44	iso-pentyl	Ph-	8-SCH_2CH_3
45	iso-pentyl	Ph-	8-NH_2
46	iso-pentyl	Ph-	8-NHOH
47	iso-pentyl	Ph-	8-$NHCH_3$
48	iso-pentyl	Ph-	8-$N(CH_3)_2$
49	iso-pentyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	iso-pentyl	Ph-	8-$NHC(=O)CH_3$
51	iso-pentyl	Ph-	8-$N(CH_2CH_3)_2$
52	iso-pentyl	Ph-	8-$NMeCH_2CO_2H$
53	iso-pentyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	iso-pentyl	Ph-	8-(N)-morpholine
55	iso-pentyl	Ph-	8-(N)-azetidine
56	iso-pentyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	iso-pentyl	Ph-	8-(N)-pyrrolidine
58	iso-pentyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	iso-pentyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	iso-pentyl	Ph-	8-(N)-N'-methylpiperazine
61	iso-pentyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-

62	iso-pentyl	Ph-	8-NH-CBZ
63	iso-pentyl	Ph-	8-NHC(O)C_5H_{11}
64	iso-pentyl	Ph-	8-NHC(O)CH_2Br
65	iso-pentyl	Ph-	8-NH-C(NH)NH_2
66	iso-pentyl	Ph-	8-(2)-thiophene
67	iso-pentyl	Ph-	9-methyl
68	iso-pentyl	Ph-	9-ethyl
69	iso-pentyl	Ph-	9-iso-propyl
70	iso-pentyl	Ph-	9-tert-butyl
71	iso-pentyl	Ph-	9-OH
72	iso-pentyl	Ph-	9-OCH_3
73	iso-pentyl	Ph-	9-O(iso-propyl)
74	iso-pentyl	Ph-	9-SCH_3
75	iso-pentyl	Ph-	9-$SOCH_3$
76	iso-pentyl	Ph-	9-SO_2CH_3
77	iso-pentyl	Ph-	9-SCH_2CH_3
78	iso-pentyl	Ph-	9-NH_2
79	iso-pentyl	Ph-	9-NHOH
80	iso-pentyl	Ph-	9-$NHCH_3$
81	iso-pentyl	Ph-	9-$N(CH_3)_2$
82	iso-pentyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	iso-pentyl	Ph-	9-NHC(=O)CH_3
84	iso-pentyl	Ph-	9-$N(CH_2CH_3)_2$
85	iso-pentyl	Ph-	9-$NMeCH_2CO_2H$
86	iso-pentyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	iso-pentyl	Ph-	9-(N)-morpholine
88	iso-pentyl	Ph-	9-(N)-azetidine
89	iso-pentyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	iso-pentyl	Ph-	9-(N)-pyrrolidine
91	iso-pentyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	iso-pentyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	iso-pentyl	Ph-	9-(N)-N′-methylpiperazine
93	iso-pentyl	Ph-	9-(N)-N′-dimethylpiperazinium, I^-
95	iso-pentyl	Ph-	9-NH-CBZ
96	iso-pentyl	Ph-	9-NHC(O)C_5H_{11}
97	iso-pentyl	Ph-	9-NHC(O)CH_2Br
98	iso-pentyl	Ph-	9-NH-C(NH)NH_2
99	iso-pentyl	Ph-	9-(2)-thiophene
100	iso-pentyl	Ph-	7-OCH_3, 8-OCH_3
101	iso-pentyl	Ph-	7-SCH_3, 8-OCH_3
102	iso-pentyl	Ph-	7-SCH_3, 8-SCH_3

	103	iso-pentyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.009	01	$CH_2C(=O)C_2H_5$	Ph-	7-methyl
	02	$CH_2C(=O)C_2H_5$	Ph-	7-ethyl
	03	$CH_2C(=O)C_2H_5$	Ph-	7-iso-propyl
	04	$CH_2C(=O)C_2H_5$	Ph-	7-tert-butyl
	05	$CH_2C(=O)C_2H_5$	Ph-	7-OH
	06	$CH_2C(=O)C_2H_5$	Ph-	7-OCH_3
	07	$CH_2C(=O)C_2H_5$	Ph-	7-O(iso-propyl)
	08	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_3
	09	$CH_2C(=O)C_2H_5$	Ph-	7-$SOCH_3$
	10	$CH_2C(=O)C_2H_5$	Ph-	7-SO_2CH_3
	11	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_2CH_3
	12	$CH_2C(=O)C_2H_5$	Ph-	7-NH_2
	13	$CH_2C(=O)C_2H_5$	Ph-	7-NHOH
	14	$CH_2C(=O)C_2H_5$	Ph-	7-$NHCH_3$
	15	$CH_2C(=O)C_2H_5$	Ph-	7-$N(CH_3)_2$
	16	$CH_2C(=O)C_2H_5$	Ph-	7-$N^+(CH_3)_3$, I^-
	17	$CH_2C(=O)C_2H_5$	Ph-	7-$NHC(=O)CH_3$
	18	$CH_2C(=O)C_2H_5$	Ph-	7-$N(CH_2CH_3)_2$
	19	$CH_2C(=O)C_2H_5$	Ph-	7-$NMeCH_2CO_2H$
	20	$CH_2C(=O)C_2H_5$	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-morpholine
	22	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-azetidine
	23	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N-methylazetidinium, I^-
	24	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-pyrrolidine
	25	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N'-methylpiperazine
	28	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	$CH_2C(=O)C_2H_5$	Ph-	7-NH-CBZ
	30	$CH_2C(=O)C_2H_5$	Ph-	7-$NHC(O)C_5H_{11}$
	31	$CH_2C(=O)C_2H_5$	Ph-	7-$NHC(O)CH_2Br$
	32	$CH_2C(=O)C_2H_5$	Ph-	7-$NH-C(NH)NH_2$
	33	$CH_2C(=O)C_2H_5$	Ph-	7-(2)-thiophene
	34	$CH_2C(=O)C_2H_5$	Ph-	8-methyl
	35	$CH_2C(=O)C_2H_5$	Ph-	8-ethyl
	36	$CH_2C(=O)C_2H_5$	Ph-	8-iso-propyl
	37	$CH_2C(=O)C_2H_5$	Ph-	8-tert-butyl
	38	$CH_2C(=O)C_2H_5$	Ph-	8-OH
	39	$CH_2C(=O)C_2H_5$	Ph-	8-OCH_3

40	$CH_2C(=O)C_2H_5$	Ph-	8-O(iso-propyl)
41	$CH_2C(=O)C_2H_5$	Ph-	8-SCH_3
42	$CH_2C(=O)C_2H_5$	Ph-	8-$SOCH_3$
43	$CH_2C(=O)C_2H_5$	Ph-	8-SO_2CH_3
44	$CH_2C(=O)C_2H_5$	Ph-	8-SCH_2CH_3
45	$CH_2C(=O)C_2H_5$	Ph-	8-NH_2
46	$CH_2C(=O)C_2H_5$	Ph-	8-NHOH
47	$CH_2C(=O)C_2H_5$	Ph-	8-$NHCH_3$
48	$CH_2C(=O)C_2H_5$	Ph-	8-$N(CH_3)_2$
49	$CH_2C(=O)C_2H_5$	Ph-	8-$N^+(CH_3)_3$, I^-
50	$CH_2C(=O)C_2H_5$	Ph-	8-$NHC(=O)CH_3$
51	$CH_2C(=O)C_2H_5$	Ph-	8-$N(CH_2CH_3)_2$
52	$CH_2C(=O)C_2H_5$	Ph-	8-$NMeCH_2CO_2H$
53	$CH_2C(=O)C_2H_5$	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-morpholine
55	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-azetidine
56	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N-methylazetidinium, I^-
57	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-pyrrolidine
58	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N'-methylpiperazine
61	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	$CH_2C(=O)C_2H_5$	Ph-	8-NH-CBZ
63	$CH_2C(=O)C_2H_5$	Ph-	8-$NHC(O)C_5H_{11}$
64	$CH_2C(=O)C_2H_5$	Ph-	8-$NHC(O)CH_2Br$
65	$CH_2C(=O)C_2H_5$	Ph-	8-$NH-C(NH)NH_2$
66	$CH_2C(=O)C_2H_5$	Ph-	8-(2)-thiophene
67	$CH_2C(=O)C_2H_5$	Ph-	9-methyl
68	$CH_2C(=O)C_2H_5$	Ph-	9-ethyl
69	$CH_2C(=O)C_2H_5$	Ph-	9-iso-propyl
70	$CH_2C(=O)C_2H_5$	Ph-	9-tert-butyl
71	$CH_2C(=O)C_2H_5$	Ph-	9-OH
72	$CH_2C(=O)C_2H_5$	Ph-	9-OCH_3
73	$CH_2C(=O)C_2H_5$	Ph-	9-O(iso-propyl)
74	$CH_2C(=O)C_2H_5$	Ph-	9-SCH_3
75	$CH_2C(=O)C_2H_5$	Ph-	9-$SOCH_3$
76	$CH_2C(=O)C_2H_5$	Ph-	9-SO_2CH_3
77	$CH_2C(=O)C_2H_5$	Ph-	9-SCH_2CH_3
78	$CH_2C(=O)C_2H_5$	Ph-	9-NH_2
79	$CH_2C(=O)C_2H_5$	Ph-	9-NHOH
80	$CH_2C(=O)C_2H_5$	Ph-	9-$NHCH_3$

	81	$CH_2C(=O)C_2H_5$	Ph-	9-$N(CH_3)_2$
	82	$CH_2C(=O)C_2H_5$	Ph-	9-$N^+(CH_3)_3$, I^-
	83	$CH_2C(=O)C_2H_5$	Ph-	9-$NHC(=O)CH_3$
	84	$CH_2C(=O)C_2H_5$	Ph-	9-$N(CH_2CH_3)_2$
	85	$CH_2C(=O)C_2H_5$	Ph-	9-$NMeCH_2CO_2H$
	86	$CH_2C(=O)C_2H_5$	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
	87	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-morpholine
	88	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-azetidine
	89	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N-methylazetidinium, I^-
	90	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-pyrrolidine
	91	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
	92	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N-methyl-morpholinium, I^-
	93	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N'-methylpiperazine
	93	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
	95	$CH_2C(=O)C_2H_5$	Ph-	9-NH-CBZ
	96	$CH_2C(=O)C_2H_5$	Ph-	9-$NHC(O)C_5H_{11}$
	97	$CH_2C(=O)C_2H_5$	Ph-	9-$NHC(O)CH_2Br$
	98	$CH_2C(=O)C_2H_5$	Ph-	9-$NH-C(NH)NH_2$
	99	$CH_2C(=O)C_2H_5$	Ph-	9-(2)-thiophene
	100	$CH_2C(=O)C_2H_5$	Ph-	7-OCH_3, 8-OCH_3
	101	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_3, 8-OCH_3
	102	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_3, 8-SCH_3
	103	$CH_2C(=O)C_2H_5$	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.010	01	$CH_2OC_2H_5$	Ph-	7-methyl
	02	$CH_2OC_2H_5$	Ph-	7-ethyl
	03	$CH_2OC_2H_5$	Ph-	7-iso-propyl
	04	$CH_2OC_2H_5$	Ph-	7-tert-butyl
	05	$CH_2OC_2H_5$	Ph-	7-OH
	06	$CH_2OC_2H_5$	Ph-	7-OCH_3
	07	$CH_2OC_2H_5$	Ph-	7-O(iso-propyl)
	08	$CH_2OC_2H_5$	Ph-	7-SCH_3
	09	$CH_2OC_2H_5$	Ph-	7-$SOCH_3$
	10	$CH_2OC_2H_5$	Ph-	7-SO_2CH_3
	11	$CH_2OC_2H_5$	Ph-	7-SCH_2CH_3
	12	$CH_2OC_2H_5$	Ph-	7-NH_2
	13	$CH_2OC_2H_5$	Ph-	7-NHOH
	14	$CH_2OC_2H_5$	Ph-	7-$NHCH_3$
	15	$CH_2OC_2H_5$	Ph-	7-$N(CH_3)_2$
	16	$CH_2OC_2H_5$	Ph-	7-$N^+(CH_3)_3$, I^-

17	$CH_2OC_2H_5$	Ph-	7-NHC(=O)CH_3
18	$CH_2OC_2H_5$	Ph-	$\text{7-N(CH}_2\text{CH}_3)_2$
19	$CH_2OC_2H_5$	Ph-	$\text{7-NMeCH}_2\text{CO}_2\text{H}$
20	$CH_2OC_2H_5$	Ph-	$\text{7-N}^+\text{(Me)}_2\text{CH}_2\text{CO}_2\text{H, I}^-$
21	$CH_2OC_2H_5$	Ph-	7-(N)-morpholine
22	$CH_2OC_2H_5$	Ph-	7-(N)-azetidine
23	$CH_2OC_2H_5$	Ph-	7-(N)-N-methylazetidinium, I^-
24	$CH_2OC_2H_5$	Ph-	7-(N)-pyrrolidine
25	$CH_2OC_2H_5$	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	$CH_2OC_2H_5$	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	$CH_2OC_2H_5$	Ph-	7-(N)-N'-methylpiperazine
28	$CH_2OC_2H_5$	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	$CH_2OC_2H_5$	Ph-	7-NH-CBZ
30	$CH_2OC_2H_5$	Ph-	$\text{7-NHC(O)C}_5\text{H}_{11}$
31	$CH_2OC_2H_5$	Ph-	$\text{7-NHC(O)CH}_2\text{Br}$
32	$CH_2OC_2H_5$	Ph-	7-NH-C(NH)NH_2
33	$CH_2OC_2H_5$	Ph-	7-(2)-thiophene
34	$CH_2OC_2H_5$	Ph-	8-methyl
35	$CH_2OC_2H_5$	Ph-	8-ethyl
36	$CH_2OC_2H_5$	Ph-	8-iso-propyl
37	$CH_2OC_2H_5$	Ph-	8-tert-butyl
38	$CH_2OC_2H_5$	Ph-	8-OH
39	$CH_2OC_2H_5$	Ph-	8-OCH_3
40	$CH_2OC_2H_5$	Ph-	8-O(iso-propyl)
41	$CH_2OC_2H_5$	Ph-	8-SCH_3
42	$CH_2OC_2H_5$	Ph-	8-SOCH_3
43	$CH_2OC_2H_5$	Ph-	$\text{8-SO}_2\text{CH}_3$
44	$CH_2OC_2H_5$	Ph-	$\text{8-SCH}_2\text{CH}_3$
45	$CH_2OC_2H_5$	Ph-	8-NH_2
46	$CH_2OC_2H_5$	Ph-	8-NHOH
47	$CH_2OC_2H_5$	Ph-	8-NHCH_3
48	$CH_2OC_2H_5$	Ph-	$\text{8-N(CH}_3)_2$
49	$CH_2OC_2H_5$	Ph-	$\text{8-N}^+\text{(CH}_3)_3\text{, I}^-$
50	$CH_2OC_2H_5$	Ph-	8-NHC(=O)CH_3
51	$CH_2OC_2H_5$	Ph-	$\text{8-N(CH}_2\text{CH}_3)_2$
52	$CH_2OC_2H_5$	Ph-	$\text{8-NMeCH}_2\text{CO}_2\text{H}$
53	$CH_2OC_2H_5$	Ph-	$\text{8-N}^+\text{(Me)}_2\text{CH}_2\text{CO}_2\text{H, I}^-$
54	$CH_2OC_2H_5$	Ph-	8-(N)-morpholine
55	$CH_2OC_2H_5$	Ph-	8-(N)-azetidine
56	$CH_2OC_2H_5$	Ph-	8-(N)-N-methylazetidinium, I^-

57	$CH_2OC_2H_5$	Ph-	8-(N)-pyrrolidine
58	$CH_2OC_2H_5$	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	$CH_2OC_2H_5$	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	$CH_2OC_2H_5$	Ph-	8-(N)-N'-methylpiperazine
61	$CH_2OC_2H_5$	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	$CH_2OC_2H_5$	Ph-	8-NH-CBZ
63	$CH_2OC_2H_5$	Ph-	8-NHC(O)C_5H_{11}
64	$CH_2OC_2H_5$	Ph-	8-NHC(O)CH_2Br
65	$CH_2OC_2H_5$	Ph-	8-NH-C(NH)NH_2
66	$CH_2OC_2H_5$	Ph-	8-(2)-thiophene
67	$CH_2OC_2H_5$	Ph-	9-methyl
68	$CH_2OC_2H_5$	Ph-	9-ethyl
69	$CH_2OC_2H_5$	Ph-	9-iso-propyl
70	$CH_2OC_2H_5$	Ph-	9-tert-butyl
71	$CH_2OC_2H_5$	Ph-	9-OH
72	$CH_2OC_2H_5$	Ph-	9-OCH_3
73	$CH_2OC_2H_5$	Ph-	9-O(iso-propyl)
74	$CH_2OC_2H_5$	Ph-	9-SCH_3
75	$CH_2OC_2H_5$	Ph-	9-$SOCH_3$
76	$CH_2OC_2H_5$	Ph-	9-SO_2CH_3
77	$CH_2OC_2H_5$	Ph-	9-SCH_2CH_3
78	$CH_2OC_2H_5$	Ph-	9-NH_2
79	$CH_2OC_2H_5$	Ph-	9-NHOH
80	$CH_2OC_2H_5$	Ph-	9-$NHCH_3$
81	$CH_2OC_2H_5$	Ph-	9-$N(CH_3)_2$
82	$CH_2OC_2H_5$	Ph-	9-$N^+(CH_3)_3$, I^-
83	$CH_2OC_2H_5$	Ph-	9-NHC(=O)CH_3
84	$CH_2OC_2H_5$	Ph-	9-$N(CH_2CH_3)_2$
85	$CH_2OC_2H_5$	Ph-	9-$NMeCH_2CO_2H$
86	$CH_2OC_2H_5$	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	$CH_2OC_2H_5$	Ph-	9-(N)-morpholine
88	$CH_2OC_2H_5$	Ph-	9-(N)-azetidine
89	$CH_2OC_2H_5$	Ph-	9-(N)-N-methylazetidinium, I^-
90	$CH_2OC_2H_5$	Ph-	9-(N)-pyrrolidine
91	$CH_2OC_2H_5$	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	$CH_2OC_2H_5$	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	$CH_2OC_2H_5$	Ph-	9-(N)-N'-methylpiperazine
93	$CH_2OC_2H_5$	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	$CH_2OC_2H_5$	Ph-	9-NH-CBZ
96	$CH_2OC_2H_5$	Ph-	9-NHC(O)C_5H_{11}
97	$CH_2OC_2H_5$	Ph-	9-NHC(O)CH_2Br

	98	$CH_2OC_2H_5$	Ph-	9-NH-C(NH)NH_2
	99	$CH_2OC_2H_5$	Ph-	9-(2)-thiophene
	100	$CH_2OC_2H_5$	Ph-	7-OCH_3, 8-OCH_3
	101	$CH_2OC_2H_5$	Ph-	7-SCH_3, 8-OCH_3
	102	$CH_2OC_2H_5$	Ph-	7-SCH_3, 8-SCH_3
	103	$CH_2OC_2H_5$	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.011	01	$CH_2CH(OH)C_2H_5$	Ph-	7-methyl
	02	$CH_2CH(OH)C_2H_5$	Ph-	7-ethyl
	03	$CH_2CH(OH)C_2H_5$	Ph-	7-iso-propyl
	04	$CH_2CH(OH)C_2H_5$	Ph-	7-tert-butyl
	05	$CH_2CH(OH)C_2H_5$	Ph-	7-OH
	06	$CH_2CH(OH)C_2H_5$	Ph-	7-OCH_3
	07	$CH_2CH(OH)C_2H_5$	Ph-	7-O(iso-propyl)
	08	$CH_2CH(OH)C_2H_5$	Ph-	7-SCH_3
	09	$CH_2CH(OH)C_2H_5$	Ph-	7-$SOCH_3$
	10	$CH_2CH(OH)C_2H_5$	Ph-	7-SO_2CH_3
	11	$CH_2CH(OH)C_2H_5$	Ph-	7-SCH_2CH_3
	12	$CH_2CH(OH)C_2H_5$	Ph-	7-NH_2
	13	$CH_2CH(OH)C_2H_5$	Ph-	7-NHOH
	14	$CH_2CH(OH)C_2H_5$	Ph-	7-$NHCH_3$
	15	$CH_2CH(OH)C_2H_5$	Ph-	7-$N(CH_3)_2$
	16	$CH_2CH(OH)C_2H_5$	Ph-	7-$N^+(CH_3)_3$, I^-
	17	$CH_2CH(OH)C_2H_5$	Ph-	7-NHC(=O)CH_3
	18	$CH_2CH(OH)C_2H_5$	Ph-	7-$N(CH_2CH_3)_2$
	19	$CH_2CH(OH)C_2H_5$	Ph-	7-$NMeCH_2CO_2H$
	20	$CH_2CH(OH)C_2H_5$	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-morpholine
	22	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-azetidine
	23	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N-methylazetidinium, I^-
	24	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-pyrrolidine
	25	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N'-methylpiperazine
	28	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	$CH_2CH(OH)C_2H_5$	Ph-	7-NH-CBZ
	30	$CH_2CH(OH)C_2H_5$	Ph-	7-NHC(O)C_5H_{11}
	31	$CH_2CH(OH)C_2H_5$	Ph-	7-NHC(O)CH_2Br
	32	$CH_2CH(OH)C_2H_5$	Ph-	7-NH-C(NH)NH_2
	33	$CH_2CH(OH)C_2H_5$	Ph-	7-(2)-thiophene

34	$CH_2CH(OH)C_2H_5$	Ph-	8-methyl
35	$CH_2CH(OH)C_2H_5$	Ph-	8-ethyl
36	$CH_2CH(OH)C_2H_5$	Ph-	8-iso-propyl
37	$CH_2CH(OH)C_2H_5$	Ph-	8-tert-butyl
38	$CH_2CH(OH)C_2H_5$	Ph-	8-OH
39	$CH_2CH(OH)C_2H_5$	Ph-	8-OCH_3
40	$CH_2CH(OH)C_2H_5$	Ph-	8-O(iso-propyl)
41	$CH_2CH(OH)C_2H_5$	Ph-	8-SCH_3
42	$CH_2CH(OH)C_2H_5$	Ph-	8-$SOCH_3$
43	$CH_2CH(OH)C_2H_5$	Ph-	8-SO_2CH_3
44	$CH_2CH(OH)C_2H_5$	Ph-	8-SCH_2CH_3
45	$CH_2CH(OH)C_2H_5$	Ph-	8-NH_2
46	$CH_2CH(OH)C_2H_5$	Ph-	8-NHOH
47	$CH_2CH(OH)C_2H_5$	Ph-	8-$NHCH_3$
48	$CH_2CH(OH)C_2H_5$	Ph-	8-$N(CH_3)_2$
49	$CH_2CH(OH)C_2H_5$	Ph-	8-$N^+(CH_3)_3$, I^-
50	$CH_2CH(OH)C_2H_5$	Ph-	8-$NHC(=O)CH_3$
51	$CH_2CH(OH)C_2H_5$	Ph-	8-$N(CH_2CH_3)_2$
52	$CH_2CH(OH)C_2H_5$	Ph-	8-$NMeCH_2CO_2H$
53	$CH_2CH(OH)C_2H_5$	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-morpholine
55	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-azetidine
56	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N-methylazetidinium, I^-
57	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-pyrrolidine
58	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N′-methylpiperazine
61	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N′-dimethylpiperazinium, I^-
62	$CH_2CH(OH)C_2H_5$	Ph-	8-NH-CBZ
63	$CH_2CH(OH)C_2H_5$	Ph-	8-$NHC(O)C_5H_{11}$
64	$CH_2CH(OH)C_2H_5$	Ph-	8-$NHC(O)CH_2Br$
65	$CH_2CH(OH)C_2H_5$	Ph-	8-$NH-C(NH)NH_2$
66	$CH_2CH(OH)C_2H_5$	Ph-	8-(2)-thiophene
67	$CH_2CH(OH)C_2H_5$	Ph-	9-methyl
68	$CH_2CH(OH)C_2H_5$	Ph-	9-ethyl
69	$CH_2CH(OH)C_2H_5$	Ph-	9-iso-propyl
70	$CH_2CH(OH)C_2H_5$	Ph-	9-tert-butyl
71	$CH_2CH(OH)C_2H_5$	Ph-	9-OH
72	$CH_2CH(OH)C_2H_5$	Ph-	9-OCH_3
73	$CH_2CH(OH)C_2H_5$	Ph-	9-O(iso-propyl)
74	$CH_2CH(OH)C_2H_5$	Ph-	9-SCH_3

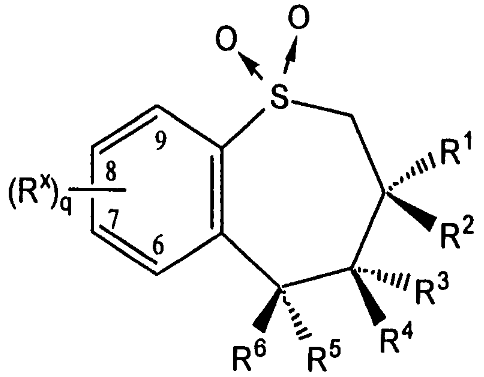
	75	$CH_2CH(OH)C_2H_5$	Ph-	9-$SOCH_3$
	76	$CH_2CH(OH)C_2H_5$	Ph-	9-SO_2CH_3
	77	$CH_2CH(OH)C_2H_5$	Ph-	9-SCH_2CH_3
	78	$CH_2CH(OH)C_2H_5$	Ph-	9-NH_2
	79	$CH_2CH(OH)C_2H_5$	Ph-	9-NHOH
	80	$CH_2CH(OH)C_2H_5$	Ph-	9-$NHCH_3$
	81	$CH_2CH(OH)C_2H_5$	Ph-	9-$N(CH_3)_2$
	82	$CH_2CH(OH)C_2H_5$	Ph-	9-$N^+(CH_3)_3$, I^-
	83	$CH_2CH(OH)C_2H_5$	Ph-	9-$NHC(=O)CH_3$
	84	$CH_2CH(OH)C_2H_5$	Ph-	9-$N(CH_2CH_3)_2$
	85	$CH_2CH(OH)C_2H_5$	Ph-	9-$NMeCH_2CO_2H$
	86	$CH_2CH(OH)C_2H_5$	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
	87	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-morpholine
	88	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-azetidine
	89	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N-methylazetidinium, I^-
	90	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-pyrrolidine
	91	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
	92	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N-methyl-morpholinium, I^-
	93	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N'-methylpiperazine
	93	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
	95	$CH_2CH(OH)C_2H_5$	Ph-	9-NH-CBZ
	96	$CH_2CH(OH)C_2H_5$	Ph-	9-$NHC(O)C_5H_{11}$
	97	$CH_2CH(OH)C_2H_5$	Ph-	9-$NHC(O)CH_2Br$
	98	$CH_2CH(OH)C_2H_5$	Ph-	9-$NH-C(NH)NH_2$
	99	$CH_2CH(OH)C_2H_5$	Ph-	9-(2)-thiophene
	100	$CH_2CH(OH)C_2H_5$	Ph-	7-OCH_3, 8-OCH_3
	101	$CH_2CH(OH)C_2H_5$	Ph-	7-SCH_3, 8-OCH_3
	102	$CH_2CH(OH)C_2H_5$	Ph-	7-SCH_3, 8-SCH_3
	103	$CH_2CH(OH)C_2H_5$	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3
F101.012	01	CH_2O-(4-picoline)	Ph-	7-methyl
	02	CH_2O-(4-picoline)	Ph-	7-ethyl
	03	CH_2O-(4-picoline)	Ph-	7-iso-propyl
	04	CH_2O-(4-picoline)	Ph-	7-tert-butyl
	05	CH_2O-(4-picoline)	Ph-	7-OH
	06	CH_2O-(4-picoline)	Ph-	7-OCH_3
	07	CH_2O-(4-picoline)	Ph-	7-O(iso-propyl)
	08	CH_2O-(4-picoline)	Ph-	7-SCH_3
	09	CH_2O-(4-picoline)	Ph-	7-$SOCH_3$
	10	CH_2O-(4-picoline)	Ph-	7-SO_2CH_3
	11	CH_2O-(4-picoline)	Ph-	7-SCH_2CH_3

12	CH_2O-(4-picoline)	Ph-	7-NH_2
13	CH_2O-(4-picoline)	Ph-	7-NHOH
14	CH_2O-(4-picoline)	Ph-	7-$NHCH_3$
15	CH_2O-(4-picoline)	Ph-	7-$N(CH_3)_2$
16	CH_2O-(4-picoline)	Ph-	7-$N^+(CH_3)_3$, I^-
17	CH_2O-(4-picoline)	Ph-	7-$NHC(=O)CH_3$
18	CH_2O-(4-picoline)	Ph-	7-$N(CH_2CH_3)_2$
19	CH_2O-(4-picoline)	Ph-	7-$NMeCH_2CO_2H$
20	CH_2O-(4-picoline)	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	CH_2O-(4-picoline)	Ph-	7-(N)-morpholine
22	CH_2O-(4-picoline)	Ph-	7-(N)-azetidine
23	CH_2O-(4-picoline)	Ph-	7-(N)-N-methylazetidinium, I^-
24	CH_2O-(4-picoline)	Ph-	7-(N)-pyrrolidine
25	CH_2O-(4-picoline)	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	CH_2O-(4-picoline)	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	CH_2O-(4-picoline)	Ph-	7-(N)-N'-methylpiperazine
28	CH_2O-(4-picoline)	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	CH_2O-(4-picoline)	Ph-	7-NH-CBZ
30	CH_2O-(4-picoline)	Ph-	7-$NHC(O)C_5H_{11}$
31	CH_2O-(4-picoline)	Ph-	7-$NHC(O)CH_2Br$
32	CH_2O-(4-picoline)	Ph-	7-NH-$C(NH)NH_2$
33	CH_2O-(4-picoline)	Ph-	7-(2)-thiophene
34	CH_2O-(4-picoline)	Ph-	8-methyl
35	CH_2O-(4-picoline)	Ph-	8-ethyl
36	CH_2O-(4-picoline)	Ph-	8-iso-propyl
37	CH_2O-(4-picoline)	Ph-	8-tert-butyl
38	CH_2O-(4-picoline)	Ph-	8-OH
39	CH_2O-(4-picoline)	Ph-	8-OCH_3
40	CH_2O-(4-picoline)	Ph-	8-O(iso-propyl)
41	CH_2O-(4-picoline)	Ph-	8-SCH_3
42	CH_2O-(4-picoline)	Ph-	8-$SOCH_3$
43	CH_2O-(4-picoline)	Ph-	8-SO_2CH_3
44	CH_2O-(4-picoline)	Ph-	8-SCH_2CH_3
45	CH_2O-(4-picoline)	Ph-	8-NH_2
46	CH_2O-(4-picoline)	Ph-	8-NHOH
47	CH_2O-(4-picoline)	Ph-	8-$NHCH_3$
48	CH_2O-(4-picoline)	Ph-	8-$N(CH_3)_2$
49	CH_2O-(4-picoline)	Ph-	8-$N^+(CH_3)_3$, I^-
50	CH_2O-(4-picoline)	Ph-	8-$NHC(=O)CH_3$
51	CH_2O-(4-picoline)	Ph-	8-$N(CH_2CH_3)_2$

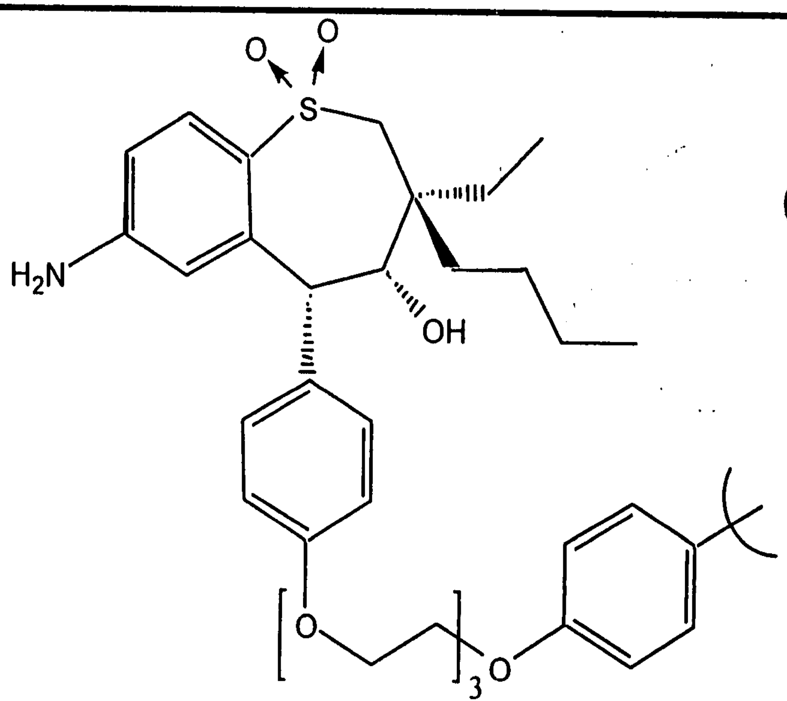
52	CH_2O-(4-picoline)	Ph-	8-$NMeCH_2CO_2H$
53	CH_2O-(4-picoline)	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	CH_2O-(4-picoline)	Ph-	8-(N)-morpholine
55	CH_2O-(4-picoline)	Ph-	8-(N)-azetidine
56	CH_2O-(4-picoline)	Ph-	8-(N)-N-methylazetidinium, I^-
57	CH_2O-(4-picoline)	Ph-	8-(N)-pyrrolidine
58	CH_2O-(4-picoline)	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	CH_2O-(4-picoline)	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	CH_2O-(4-picoline)	Ph-	8-(N)-N'-methylpiperazine
61	CH_2O-(4-picoline)	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	CH_2O-(4-picoline)	Ph-	8-NH-CBZ
63	CH_2O-(4-picoline)	Ph-	8-$NHC(O)C_5H_{11}$
64	CH_2O-(4-picoline)	Ph-	8-$NHC(O)CH_2Br$
65	CH_2O-(4-picoline)	Ph-	8-$NH-C(NH)NH_2$
66	CH_2O-(4-picoline)	Ph-	8-(2)-thiophene
67	CH_2O-(4-picoline)	Ph-	9-methyl
68	CH_2O-(4-picoline)	Ph-	9-ethyl
69	CH_2O-(4-picoline)	Ph-	9-iso-propyl
70	CH_2O-(4-picoline)	Ph-	9-tert-butyl
71	CH_2O-(4-picoline)	Ph-	9-OH
72	CH_2O-(4-picoline)	Ph-	9-OCH_3
73	CH_2O-(4-picoline)	Ph-	9-O(iso-propyl)
74	CH_2O-(4-picoline)	Ph-	9-SCH_3
75	CH_2O-(4-picoline)	Ph-	9-$SOCH_3$
76	CH_2O-(4-picoline)	Ph-	9-SO_2CH_3
77	CH_2O-(4-picoline)	Ph-	9-SCH_2CH_3
78	CH_2O-(4-picoline)	Ph-	9-NH_2
79	CH_2O-(4-picoline)	Ph-	9-NHOH
80	CH_2O-(4-picoline)	Ph-	9-$NHCH_3$
81	CH_2O-(4-picoline)	Ph-	9-$N(CH_3)_2$
82	CH_2O-(4-picoline)	Ph-	9-$N^+(CH_3)_3$, I^-
83	CH_2O-(4-picoline)	Ph-	9-$NHC(=O)CH_3$
84	CH_2O-(4-picoline)	Ph-	9-$N(CH_2CH_3)_2$
85	CH_2O-(4-picoline)	Ph-	9-$NMeCH_2CO_2H$
86	CH_2O-(4-picoline)	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	CH_2O-(4-picoline)	Ph-	9-(N)-morpholine
88	CH_2O-(4-picoline)	Ph-	9-(N)-azetidine
89	CH_2O-(4-picoline)	Ph-	9-(N)-N-methylazetidinium, I^-
90	CH_2O-(4-picoline)	Ph-	9-(N)-pyrrolidine
91	CH_2O-(4-picoline)	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-

92	CH_2O-(4-picoline)	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	CH_2O-(4-picoline)	Ph-	9-(N)-N'-methylpiperazine
93	CH_2O-(4-picoline)	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	CH_2O-(4-picoline)	Ph-	9-NH-CBZ
96	CH_2O-(4-picoline)	Ph-	9-NHC(O)C_5H_{11}
97	CH_2O-(4-picoline)	Ph-	9-NHC(O)CH_2Br
98	CH_2O-(4-picoline)	Ph-	9-NH-C(NH)NH_2
99	CH_2O-(4-picoline)	Ph-	9-(2)-thiophene
100	CH_2O-(4-picoline)	Ph-	7-OCH_3, 8-OCH_3
101	CH_2O-(4-picoline)	Ph-	7-SCH_3, 8-OCH_3
102	CH_2O-(4-picoline)	Ph-	7-SCH_3, 8-SCH_3
103	CH_2O-(4-picoline)	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Additional Structures of the Present Invention



Compound Number	R^1	R^2	R^3	R^4	R^5
101	ethyl	n-butyl	OH	H	phenyl
102	ethyl	n-butyl	OH	H	phenyl
103	n-butyl	ethyl	OH	H	phenyl
104	ethyl	n-butyl	OH	H	phenyl
105	ethyl	n-butyl	OH	H	phenyl
106	ethyl	n-butyl	OH	H	phenyl
107	n-butyl	ethyl	OH	H	4-(decyloxy)phenyl
108	ethyl	n-butyl	OH	H	phenyl
109	ethyl	n-butyl	OH	H	4-(decyloxy)phenyl
110	ethyl	n-butyl	OH	H	phenyl
111	n-butyl	ethyl	OH	H	4-hydroxyphenyl

I12	ethyl	n-butyl	OH	H	
I13	ethyl	n-butyl	OH	H	4-hydroxyphenyl
I14	ethyl	n-butyl	OH	H	4-methoxyphenyl
I15	n-butyl	ethyl	OH	H	4-methoxyphenyl
I16	ethyl	n-butyl	OH	H	4-methoxyphenyl
I17	n-butyl	ethyl	OH	H	phenyl
I18	ethyl	n-butyl	OH	H	phenyl
I19	ethyl	n-butyl	OH	H	phenyl
I20	n-butyl	ethyl	OH	H	phenyl
I21	ethyl	n-butyl	OH	H	phenyl
I22	n-butyl	ethyl	OH	H	phenyl

123	ethyl	n-butyl	OH	H	phenyl
124	n-butyl	ethyl	OH	H	phenyl
125	ethyl	n-butyl	OH	H	phenyl
126	n-butyl	ethyl	OH	H	4-fluorophenyl
127	n-butyl	ethyl	OH	H	4-fluorophenyl
128	ethyl	n-butyl	OH	H	4-fluorophenyl
129	ethyl	n-butyl	OH	H	4-fluorophenyl
131	ethyl	n-butyl	OH	H	4-fluorophenyl
132	ethyl	n-butyl	OH	H	phenyl
133	ethyl	n-butyl	OH	H	phenyl
134	ethyl	n-butyl	OH	H	phenyl
135	ethyl	n-butyl	OH	H	phenyl
136	ethyl	n-butyl	OH	H	phenyl
137	n-butyl	ethyl	OH	H	phenyl
138	n-butyl	ethyl	OH	H	phenyl
139	n-butyl	ethyl	OH	H	phenyl
140					
141					
142	ethyl	n-butyl	H	OH	H
143	ethyl	n-butyl	OH	H	3-methoxyphenyl
144	ethyl	n-butyl	OH	H	4-fluorophenyl
262	ethyl	n-butyl	OH	H	3-methoxyphenyl
263	ethyl	n-butyl	H	OH	H
264	ethyl	n-butyl	OH	H	3-trifluoromethylphenyl
265	ethyl	n-butyl	H	OH	H
266	ethyl	n-butyl	OH	H	3-hydroxyphenyl
267	ethyl	n-butyl	OH	H	3-hydroxyphenyl
268	ethyl	n-butyl	OH	H	4-fluorophenyl
269	ethyl	n-butyl	H	OH	H

270	ethyl	n-butyl	OH	H	4-fluorophenyl
271	ethyl	n-butyl	OH	H	3-methoxyphenyl
272	ethyl	n-butyl	H	OH	H
273	ethyl	n-butyl	H	OH	H
274	ethyl	n-butyl	OH	H	4-fluorophenyl
275	ethyl	n-butyl	H	OH	H
276	ethyl	n-butyl	OH	H	3-methoxyphenyl
277	ethyl	n-butyl	OH	H	3-fluorophenyl
278	ethyl	n-butyl	H	OH	2-fluorophenyl
279	ethyl	n-butyl	H	OH	3-fluorophenyl
280	ethyl	n-butyl	OH	H	2-fluorophenyl
281	ethyl	n-butyl	OH	H	4-fluorophenyl
282	ethyl	n-butyl	OH	H	4-fluorophenyl
283	ethyl	n-butyl	H	OH	H
284	ethyl	n-butyl	OH	H	4-fluorophenyl
286	ethyl	ethyl	OH	H	phenyl
287	ethyl	ethyl	OH	H	phenyl
288	methyl	methyl	OH	H	phenyl
289	n-butyl	n-butyl	OH	H	phenyl
290	n-butyl	n-butyl	OH	H	phenyl
291	n-butyl	n-butyl	OH	H	phenyl
292	n-butyl	n-butyl	OH	H	4-fluorophenyl
293	n-butyl	n-butyl	OH	H	phenyl
294	n-butyl	n-butyl	OH	H	phenyl

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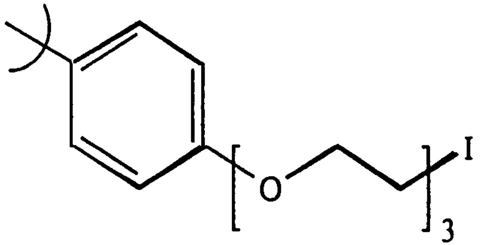
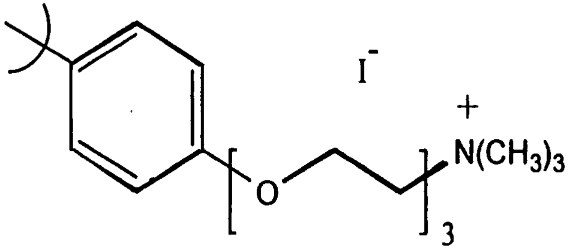
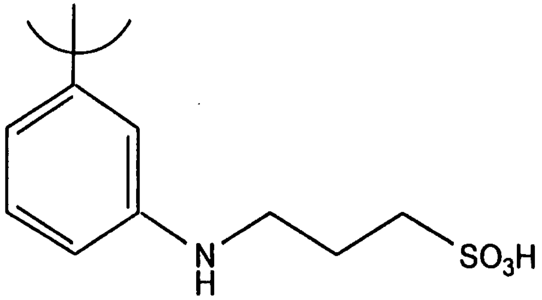
295	ethyl	n-butyl	OH	H	
296	ethyl	n-butyl	OH	H	
1000	ethyl	n-butyl	OH	H	

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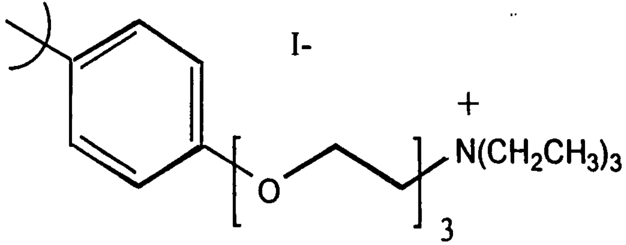
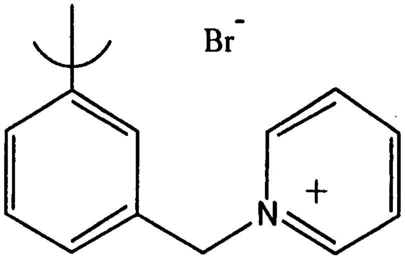
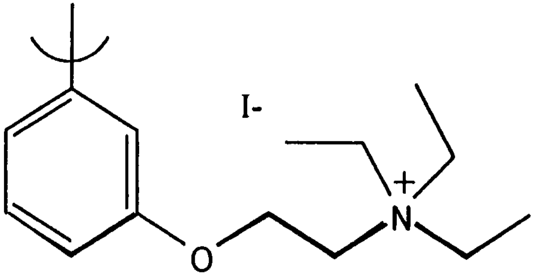
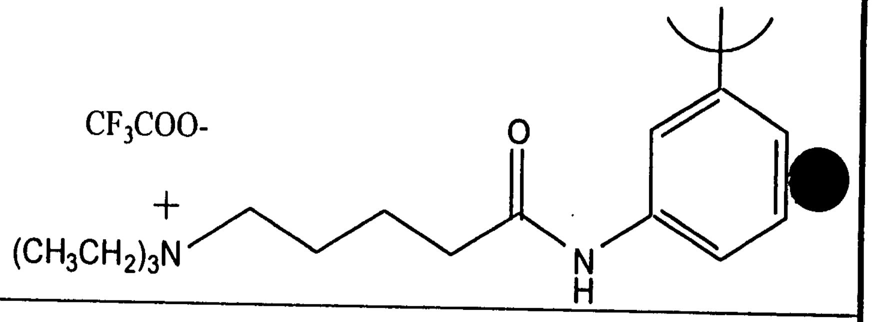
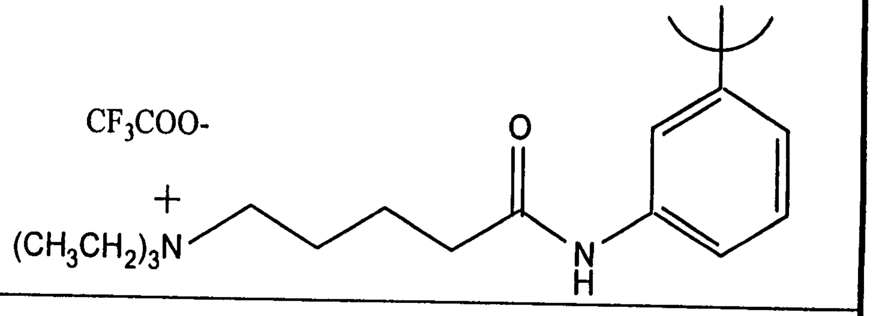
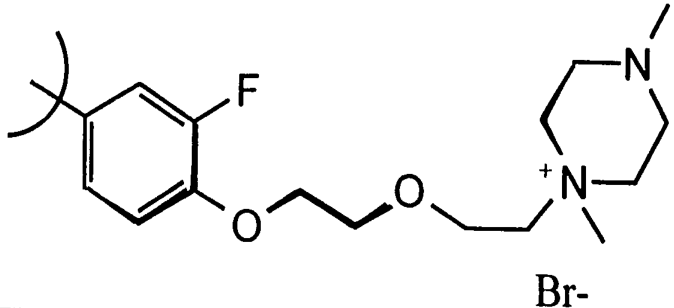
1001	ethyl	n-butyl	OH	H	 I- + N(CH2CH3)3 O 3
1002	ethyl	n-butyl	OH	H	
1003	ethyl	n-butyl	OH	H	

1004	ethyl	n-butyl	OH	H	
1005	n-butyl	n-butyl	OH	H	
1006	n-butyl	n-butyl	OH	H	

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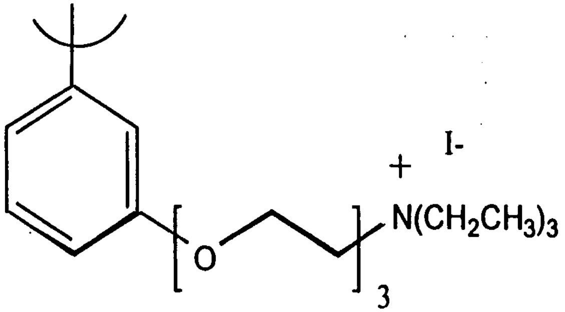
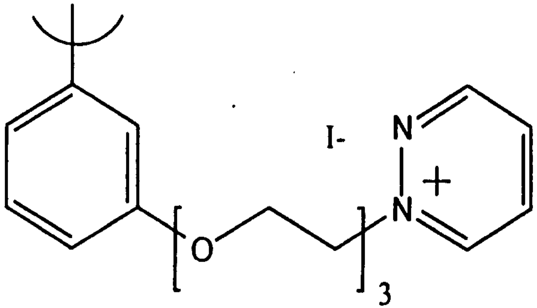
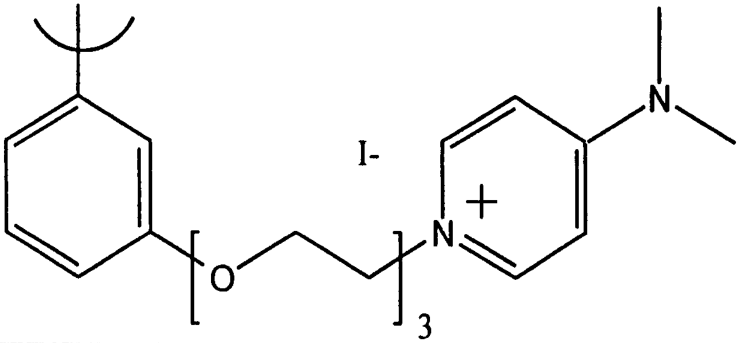
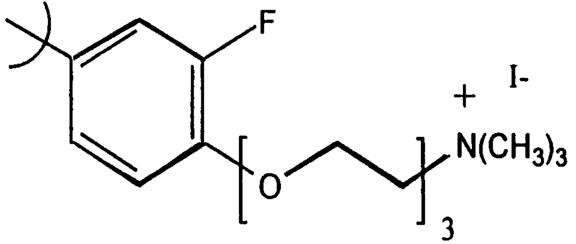
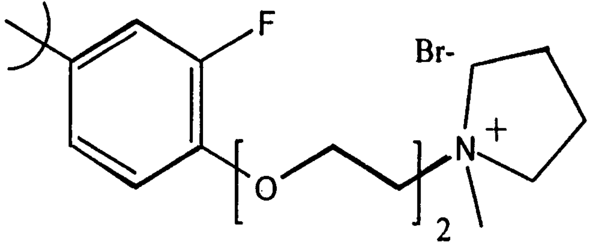
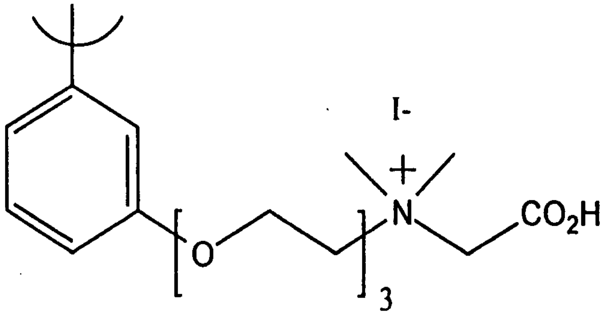
1007	n-butyl	n-butyl	OH	H	
1008	n-butyl	n-butyl	OH	H	
1009	n-butyl	n-butyl	OH	H	
1010	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl

1011	n-butyl	n-butyl	OH	H	3-fluoro-4-(5-triethylammoniumpentyloxy)phenyl, trifluoroacetate salt
1012	n-butyl	n-butyl	OH	H	4-hydroxyphenyl
1013	n-butyl	n-butyl	OH	H	
1014	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1015	n-butyl	n-butyl	OH	H	
1016	n-butyl	n-butyl	OH	H	

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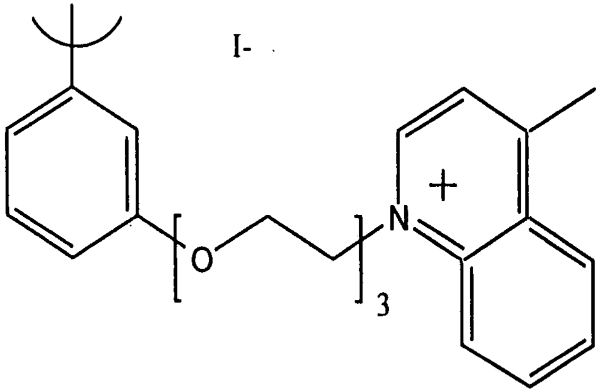
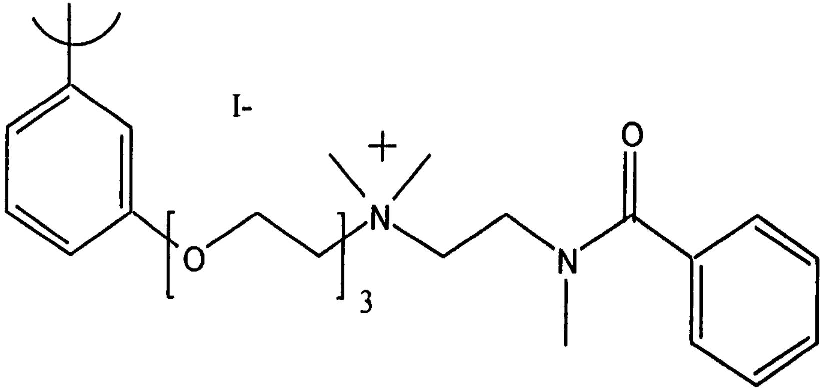
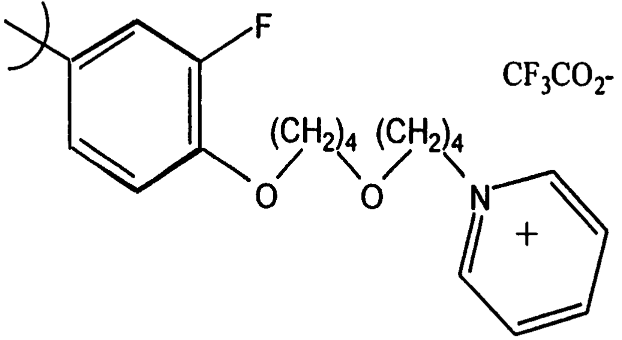
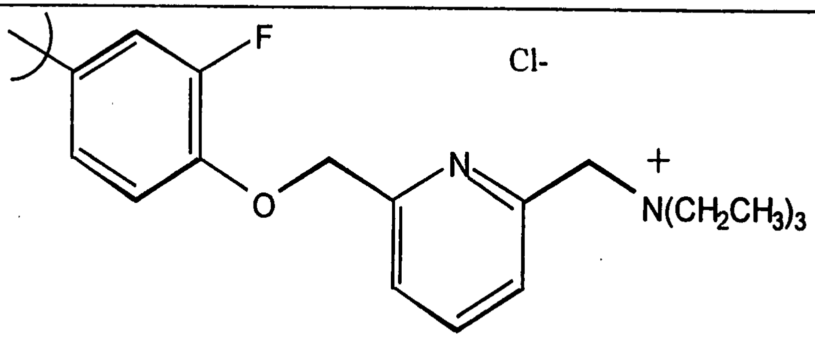
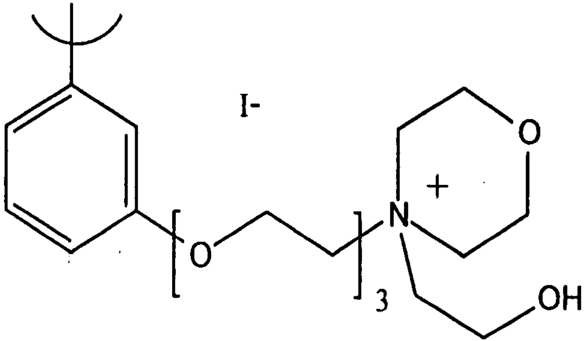
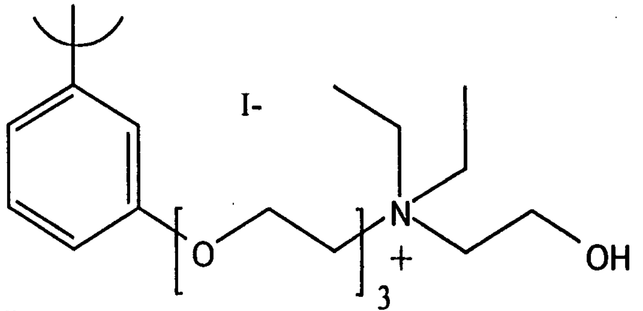
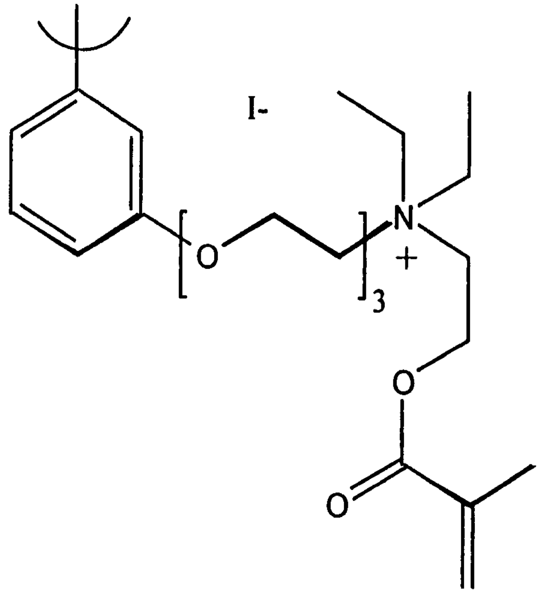
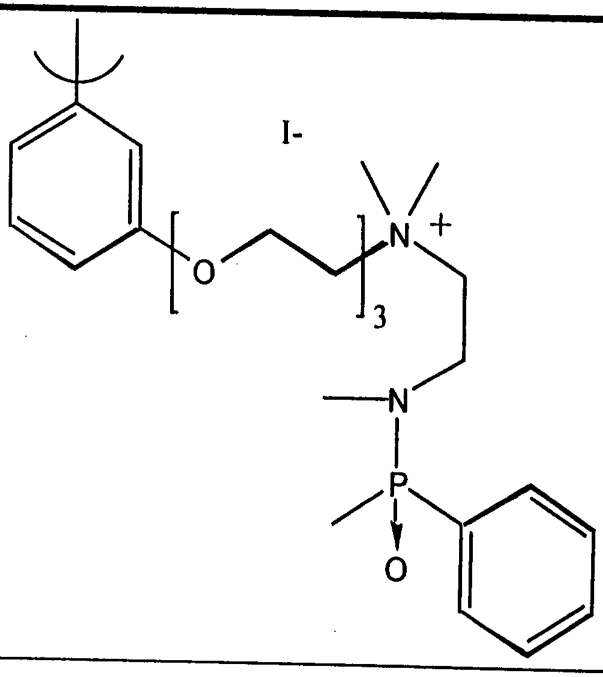
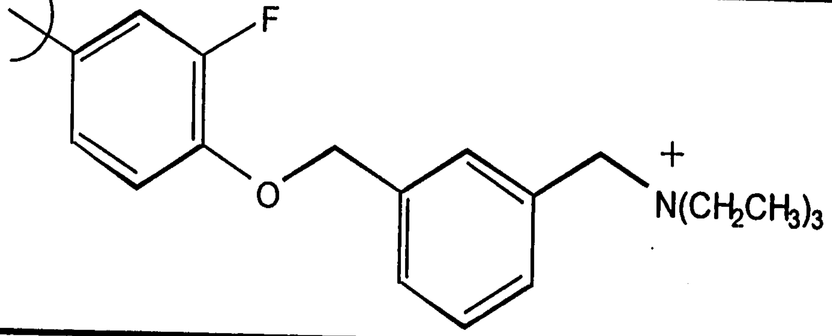
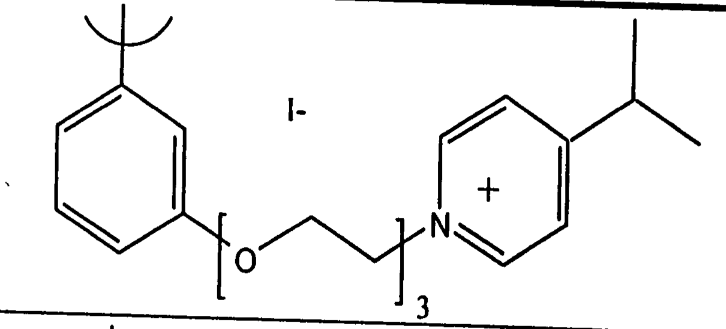
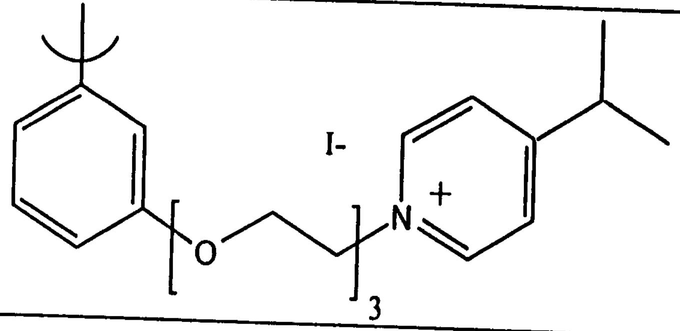
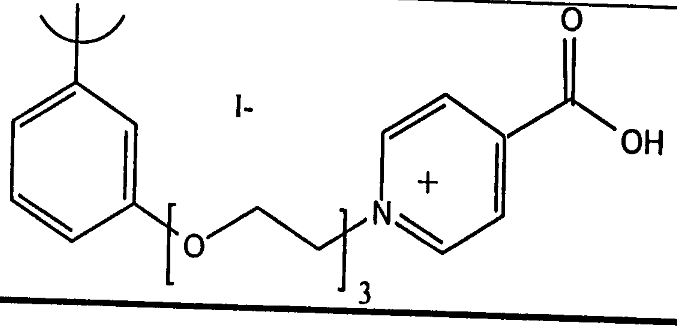
1017	n-butyl	n-butyl	OH	H	
1018	n-butyl	n-butyl	OH	H	

1019	n-butyl	n-butyl	OH	H	 F $CF_3CO_2^-$ $(CH_2)_4$ $(CH_2)_4$ O O N +
1020	n-butyl	n-butyl	OH	H	 F Cl- O N + $N(CH_2CH_3)_3$
1021	n-butyl	n-butyl	OH	H	

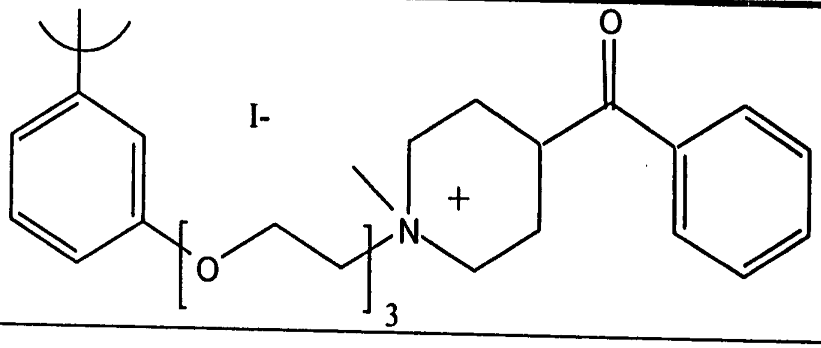
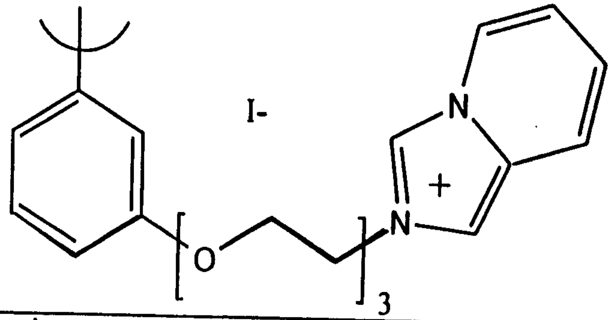
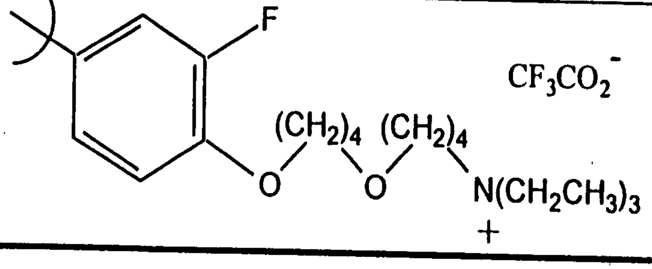
1022	n-butyl	n-butyl	OH	H	
1023	n-butyl	n-butyl	OH	H	

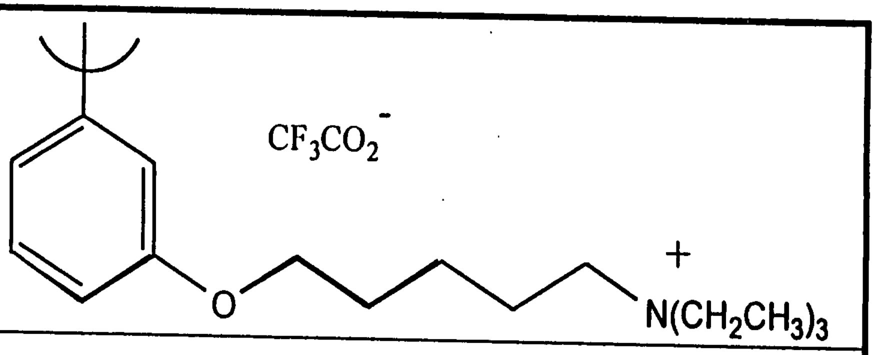
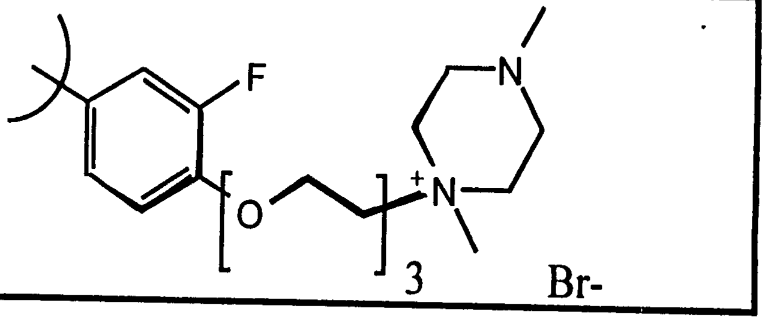
10068297.020802

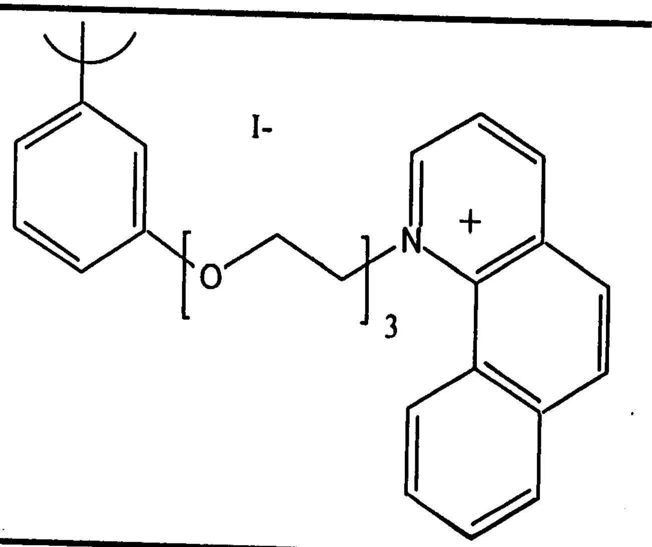
1024	n-butyl	n-butyl	OH	H	 I-
1025	n-butyl	n-butyl	OH	H	

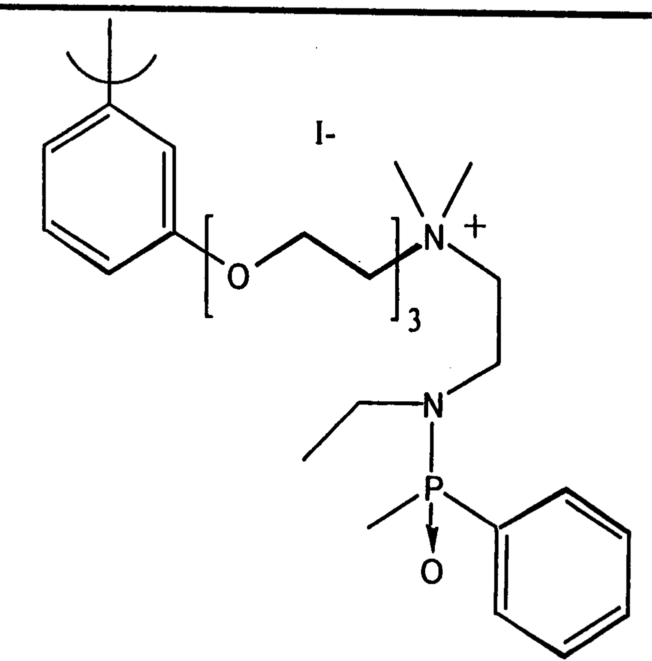
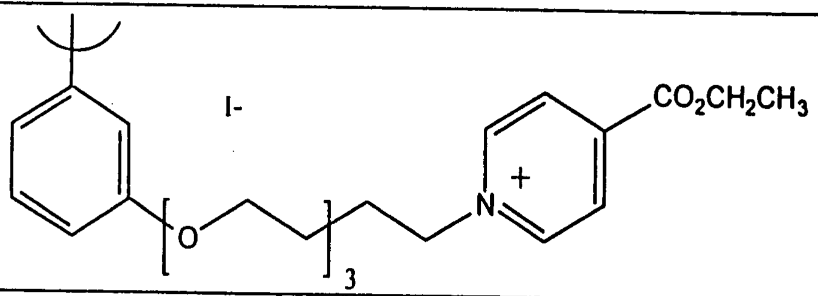
1026	n-butyl	n-butyl	OH	H	
1027	n-butyl	n-butyl	OH	H	
1028	n-butyl	n-butyl	OH	H	

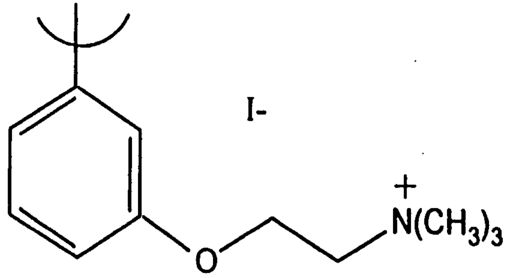
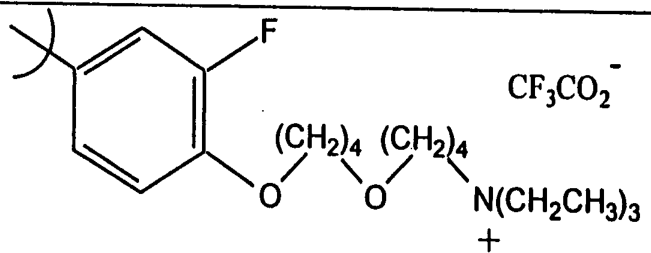
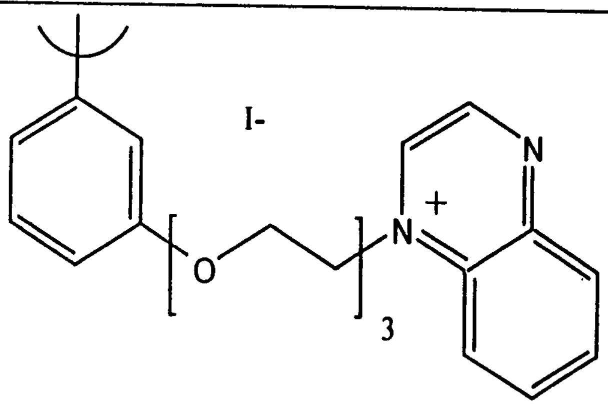
10068297 .020802

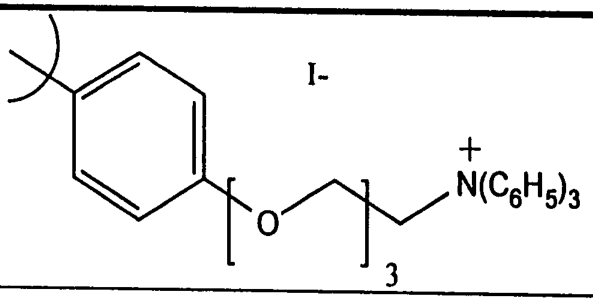
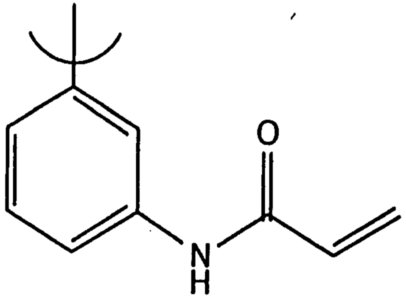
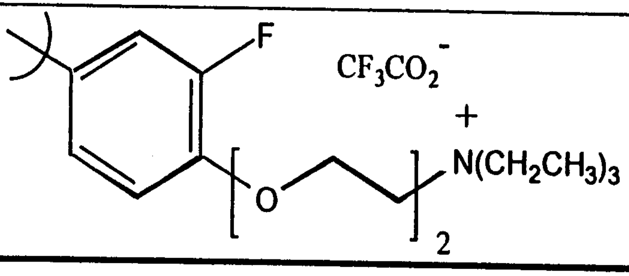
1029	n-butyl	n-butyl	OH	H	
1030	n-butyl	n-butyl	OH	H	
1031	n-butyl	n-butyl	OH	H	

1032	n-butyl	n-butyl	OH	H	 O $CF_3CO_2^-$ + $N(CH_2CH_3)_3$
1033	n-butyl	n-butyl	OH	H	

1034	n-butyl	n-butyl	OH	H	

1035	n-butyl	n-butyl	OH	H	
1036	n-butyl	n-butyl	OH	H	 I- CO2CH2CH3 + N O 3
1037	n-butyl	n-butyl	OH	H	4-hydroxyphenyl

1038	n-butyl	n-butyl	OH	H	
1039	n-butyl	n-butyl	OH	H	phenyl
1040	n-butyl	n-butyl	OH	H	 F CF3CO2 - (CH2)4 (CH2)4 O O N(CH2CH3)3 +
1041	n-butyl	n-butyl	OH	H	

1042	n-butyl	n-butyl	OH	H	
1043	n-butyl	n-butyl	OH	H	
1044	n-butyl	n-butyl	OH	H	

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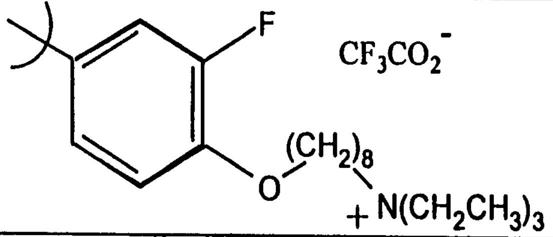
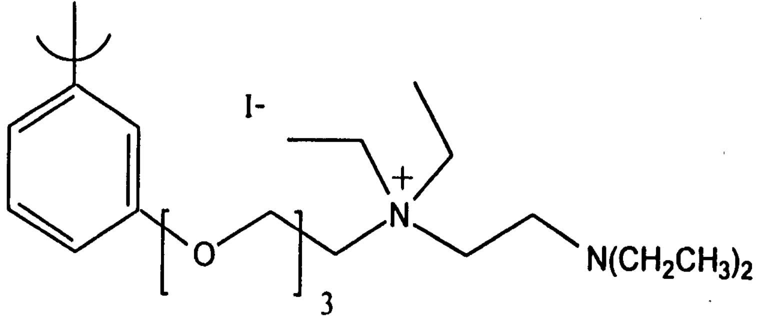
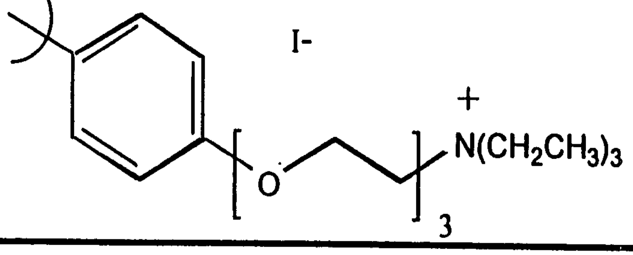
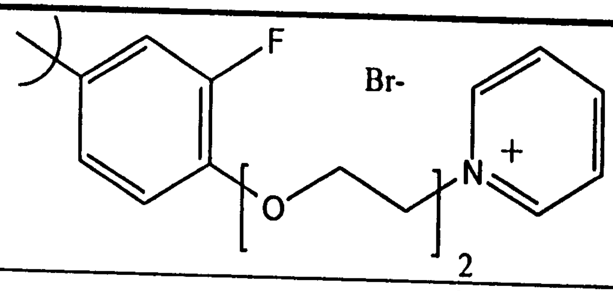
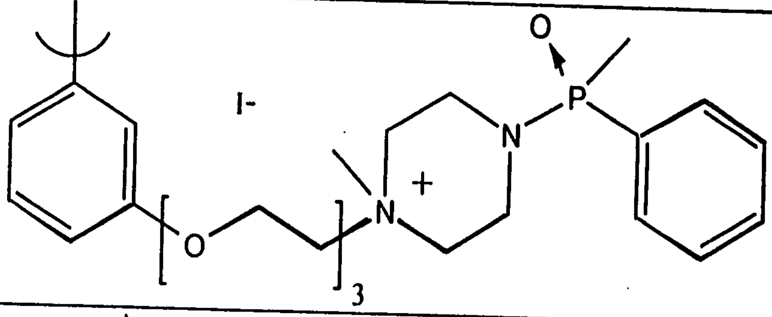
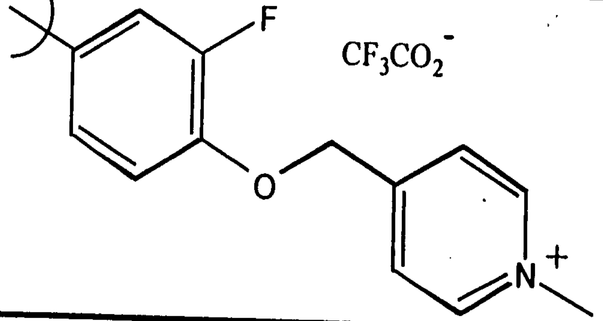
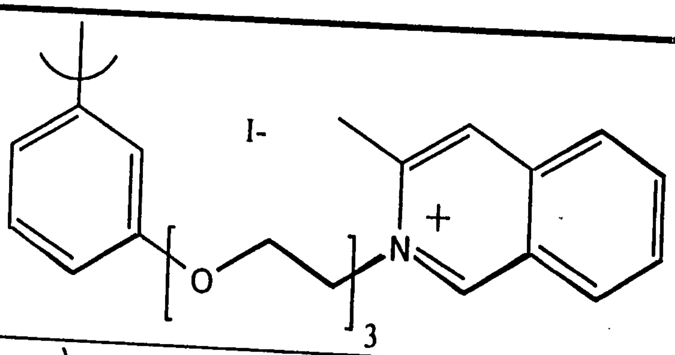
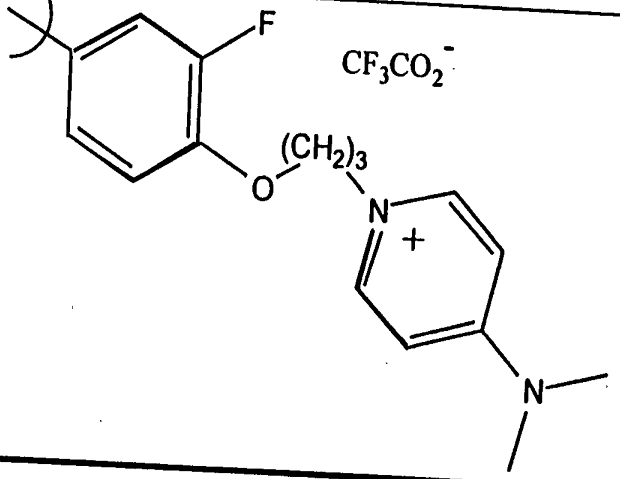
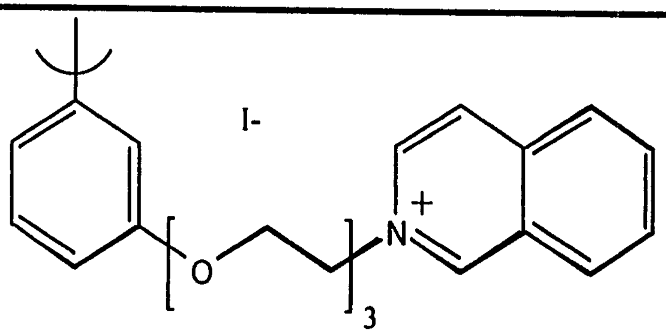
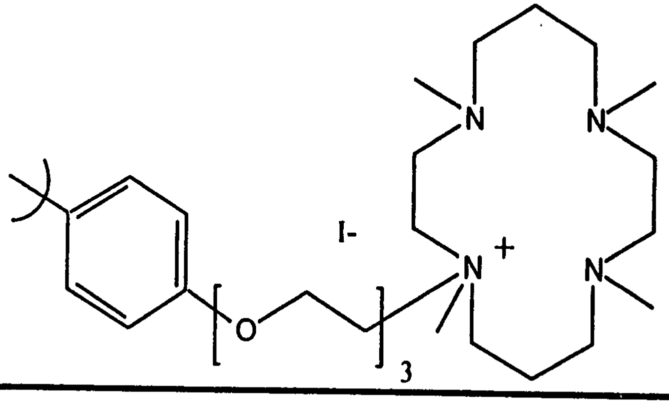
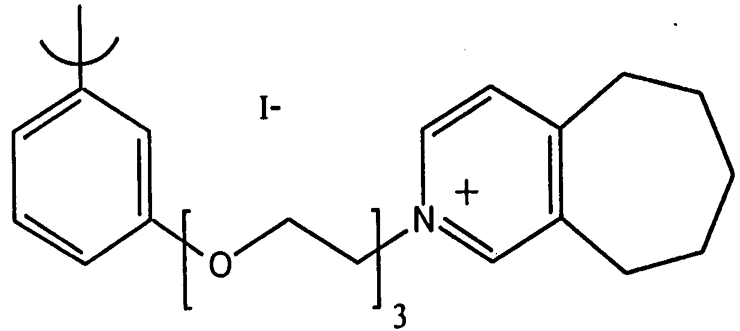
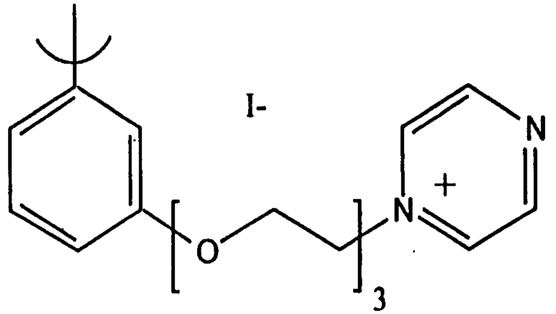
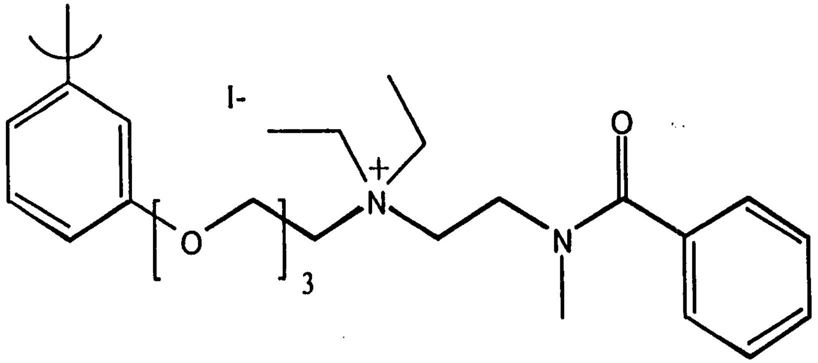
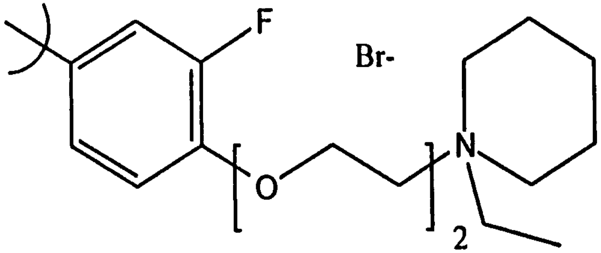
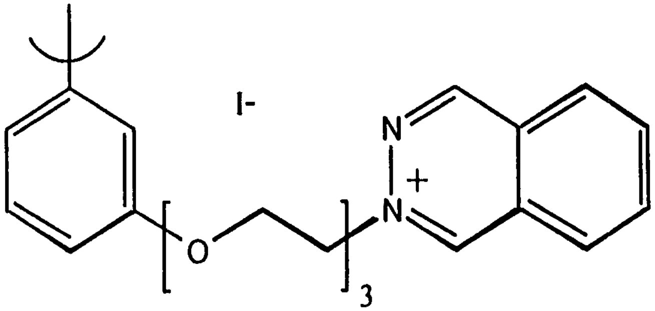
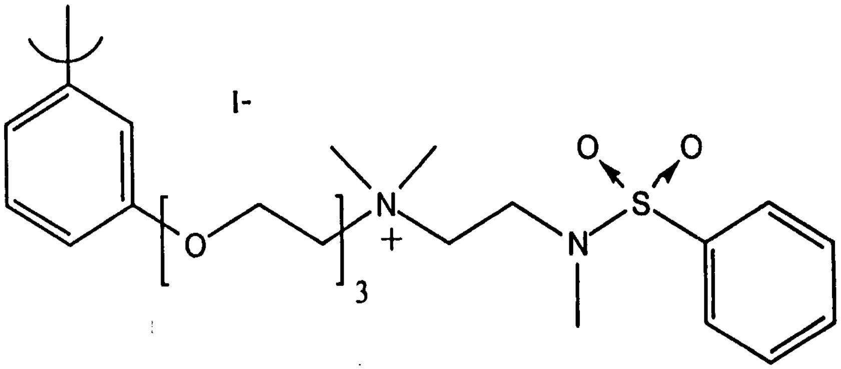
1045	n-butyl	n-butyl	OH	H	 F CF₃CO₂- O (CH2)8 + N(CH2CH3)3
1046	n-butyl	n-butyl	OH	H	3-aminophenyl
1047	n-butyl	n-butyl	OH	H	 I- + N O 3 N(CH2CH3)2
1048	n-butyl	n-butyl	OH	H	 I- + N(CH2CH3)3 O 3

1049	n-butyl	n-butyl	OH	H	
1050	n-butyl	n-butyl	OH	H	
1051	n-butyl	n-butyl	OH	H	

1052	n-butyl	n-butyl	OH	H	
1053	n-butyl	n-butyl	OH	H	

1054	n-butyl	n-butyl	OH	H	
1055	n-butyl	n-butyl	OH	H	

1056	n-butyl	n-butyl	OH	H	
1057	n-butyl	n-butyl	OH	H	
1058	n-butyl	n-butyl	OH	H	

1059	n-butyl	n-butyl	OH	H	
1060	ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1061	n-butyl	n-butyl	OH	H	
1062	n-butyl	n-butyl	OH	H	

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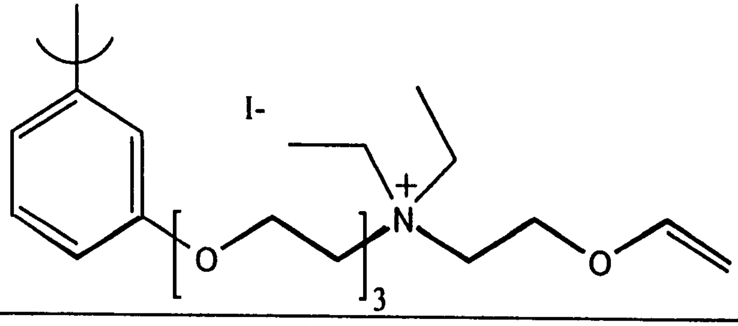
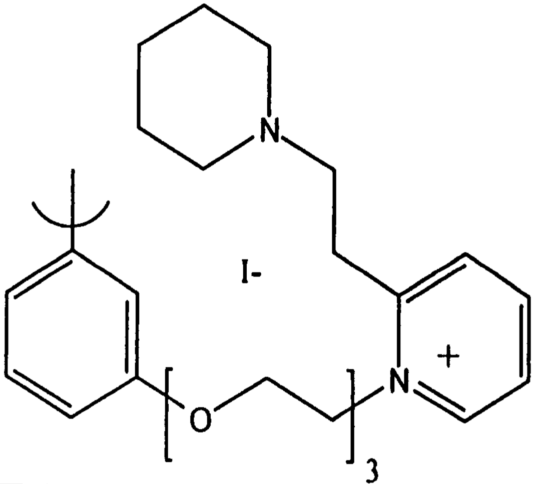
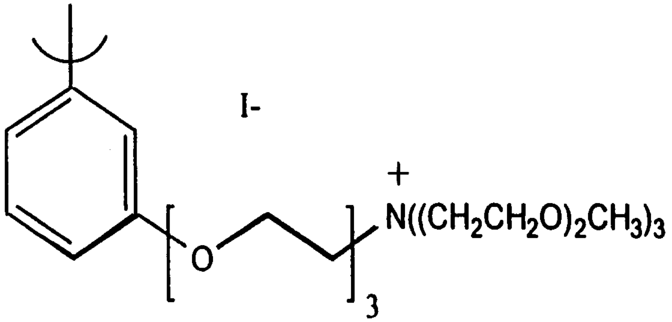
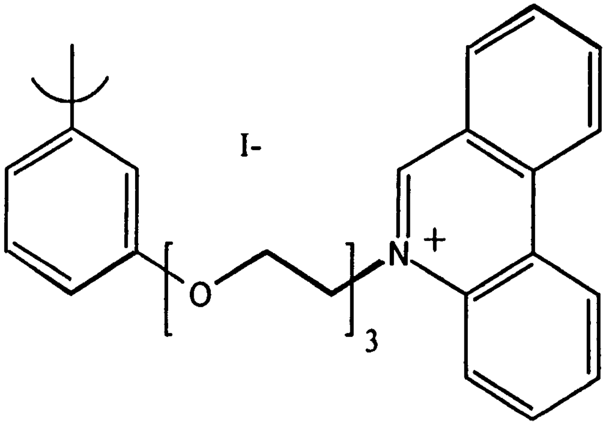
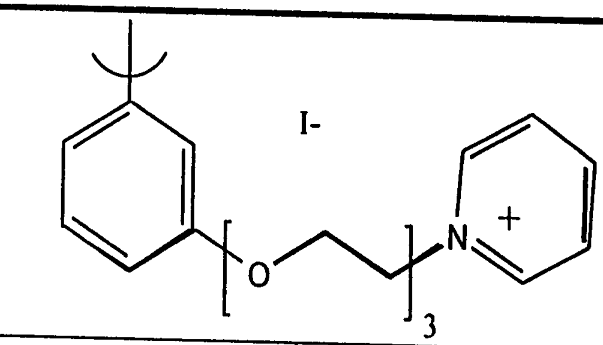
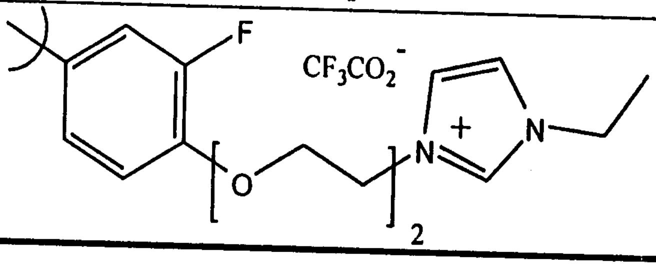
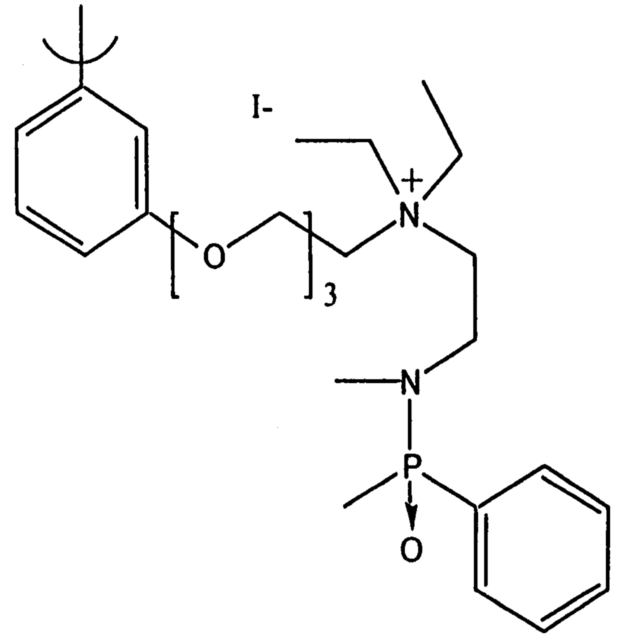
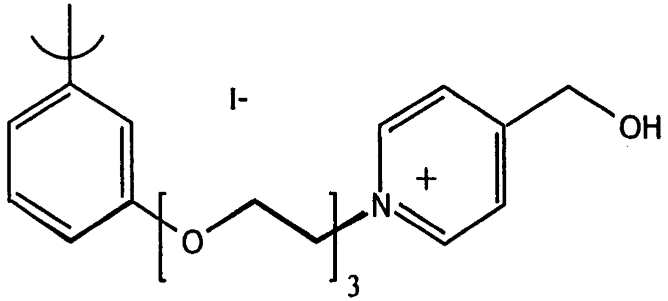
1063	n-butyl	n-butyl	OH	H	
1064	n-butyl	n-butyl	OH	H	

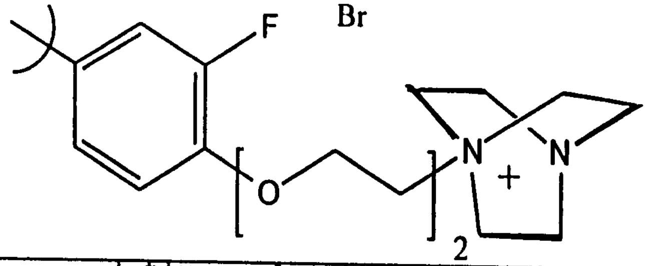
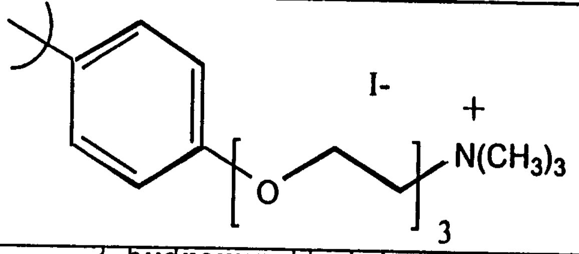
1065	n-butyl	n-butyl	OH	H	 I- + O 3 N((CH2CH2O)2CH3)3
1066	n-butyl	n-butyl	OH	H	
1067	n-butyl	n-butyl	OH	H	thiophen-3-yl

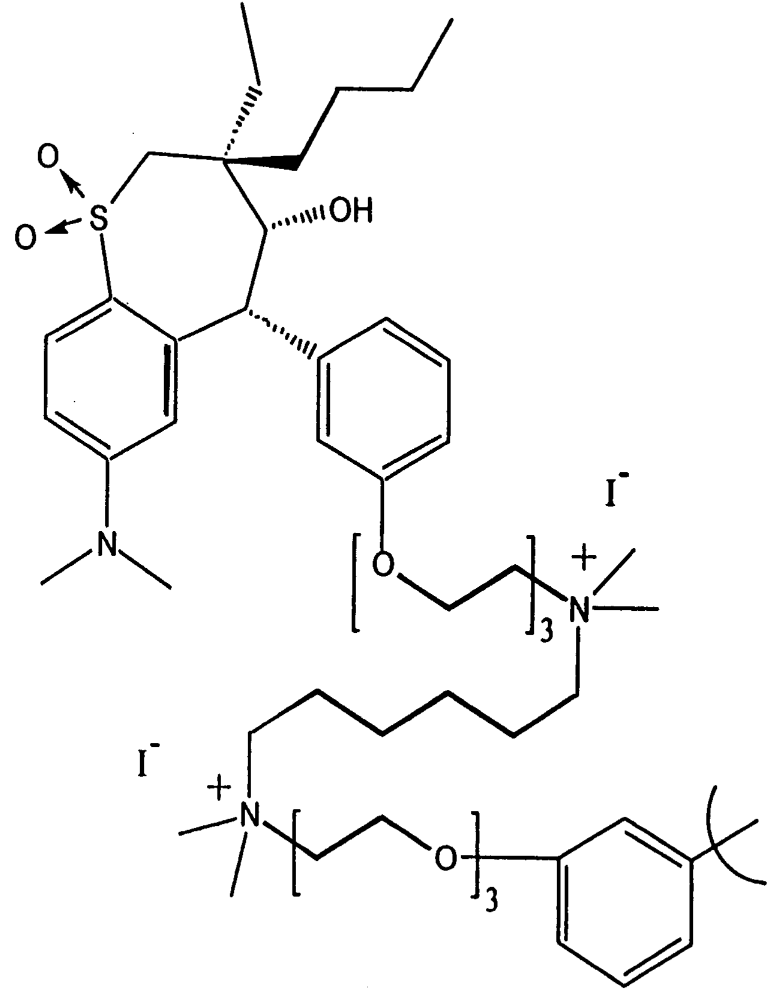
1068	n-butyl	n-butyl	OH	H	
1069	n-butyl	n-butyl	OH	H	phenyl
1070	n-butyl	n-butyl	OH	H	 F $CF_3CO_2^-$ N + N O 2

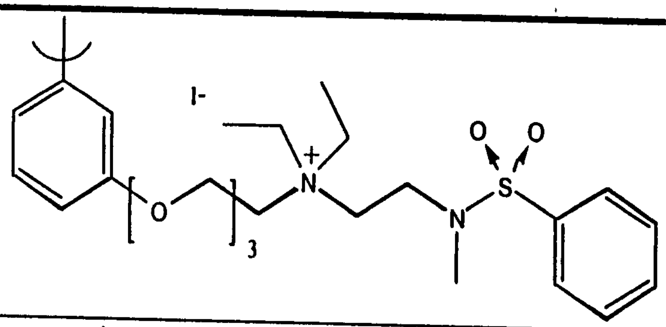
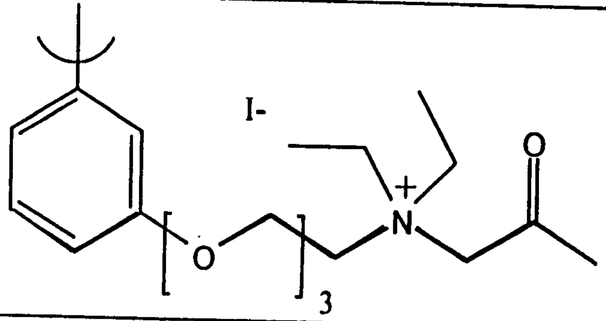
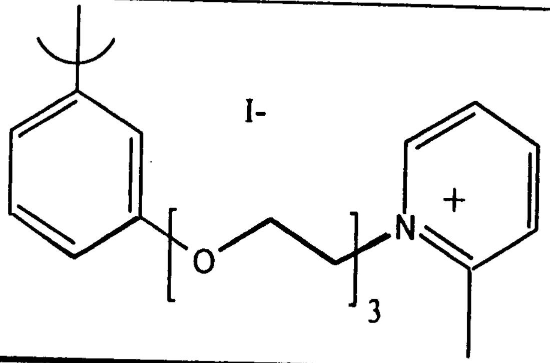
10068297 .020802

1071	n-butyl	n-butyl	OH	H	
1072	n-butyl	n-butyl	OH	H	

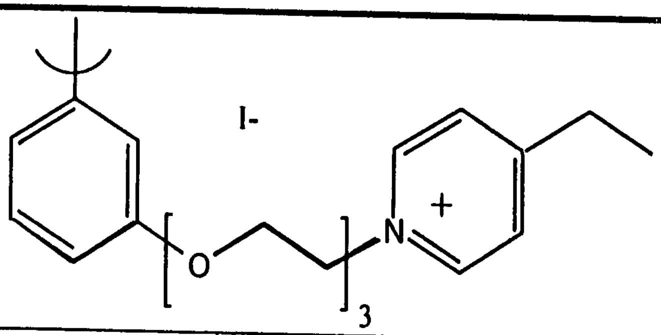
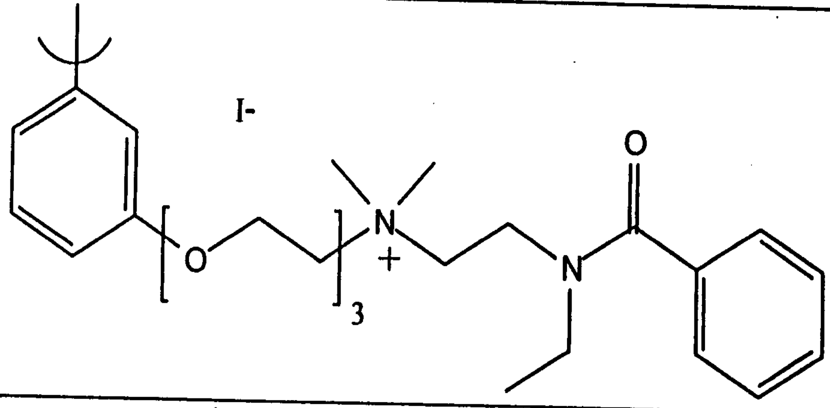
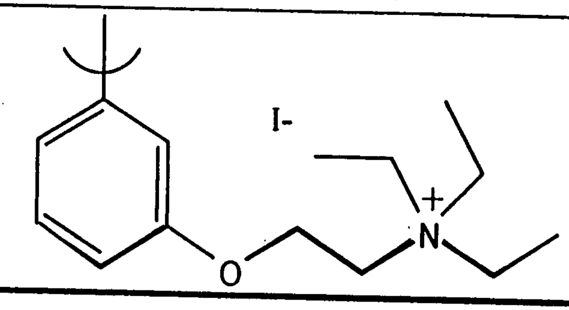
10068297.020802

1073	n-butyl	n-butyl	OH	H	
1074	ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1075	n-butyl	n-butyl	OH	H	4-fluorophenyl
1076	n-butyl	n-butyl	OH	H	
1077	n-butyl	n-butyl	OH	H	3-hydroxymethylphenyl
1078	ethyl	n-butyl	OH	H	4-hydroxyphenyl

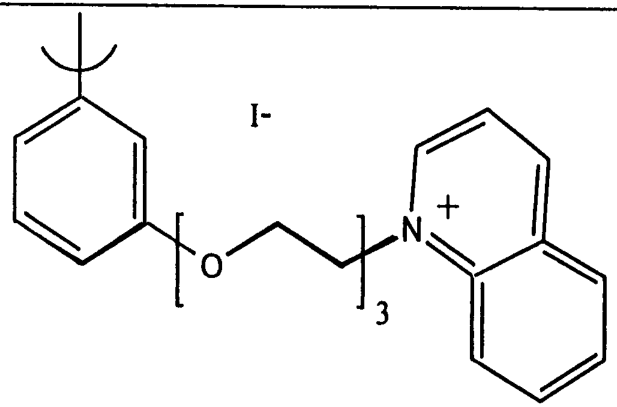
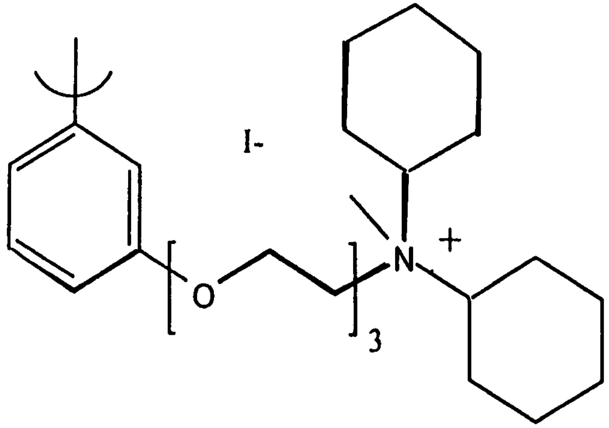
1079	ethyl	n-butyl	OH	H	 O O S OH N O 3 + N I⁻ I⁻ + N O 3

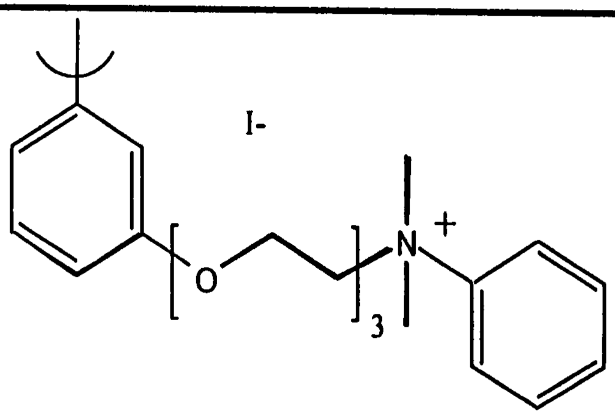
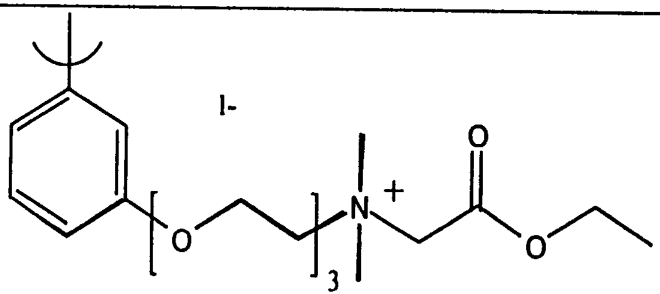
1080	n-butyl	n-butyl	OH	H	
1081	n-butyl	n-butyl	OH	H	
1082	n-butyl	n-butyl	OH	H	2-pyridyl
1083	n-butyl	n-butyl	OH	H	

10068297.020802

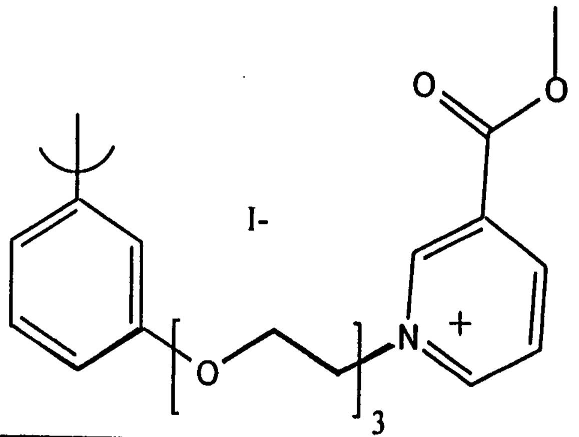
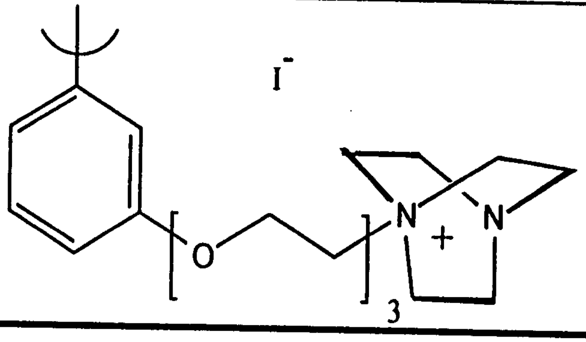
1084	n-butyl	n-butyl	OH	H	
1085	n-butyl	n-butyl	OH	H	thiophen-3-yl
1086	n-butyl	n-butyl	OH	H	
1087	n-butyl	n-butyl	OH	H	

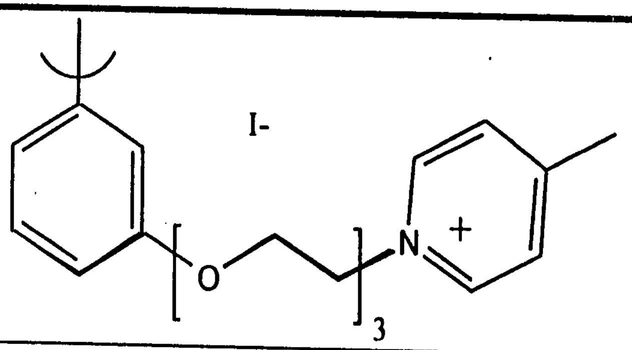
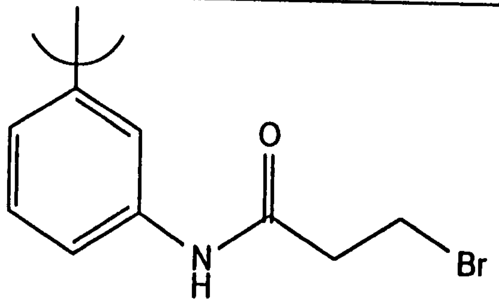
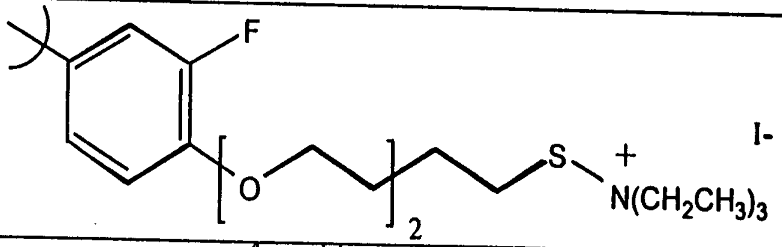
10068297 .020802

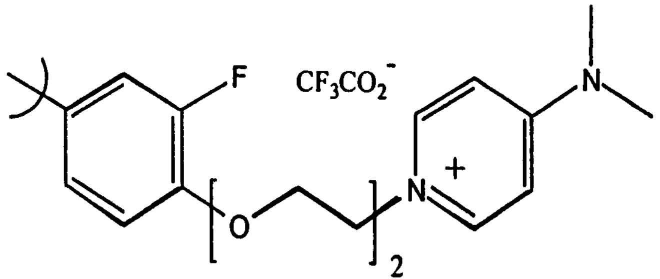
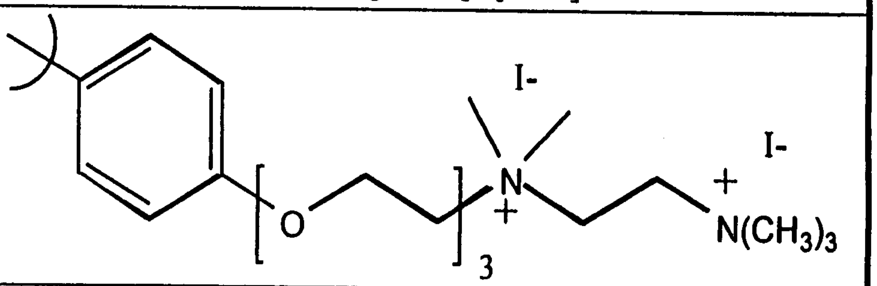
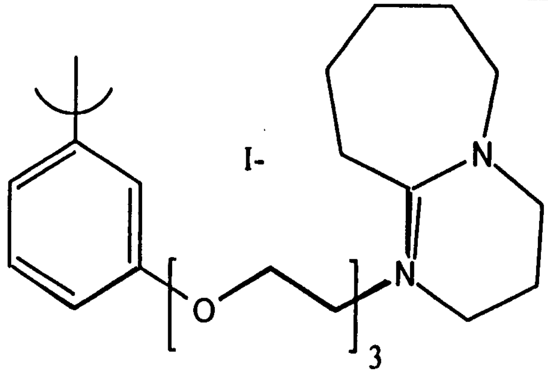
1088	ethyl	n-butyl	OH	H	3,4-methylenedioxyphenyl
1089	ethyl	n-butyl	OH	H	4-methoxyphenyl
1090	n-butyl	n-butyl	OH	H	
1091	n-butyl	n-butyl	OH	H	

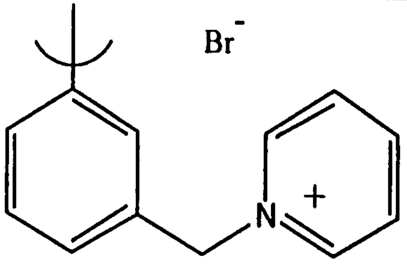
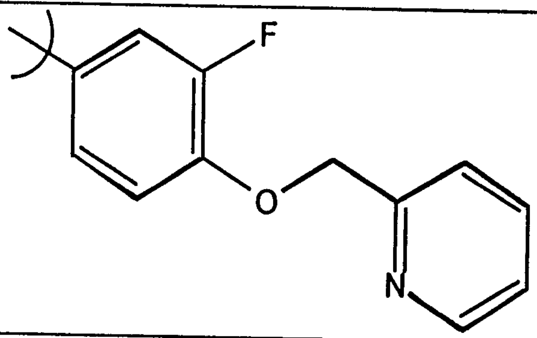
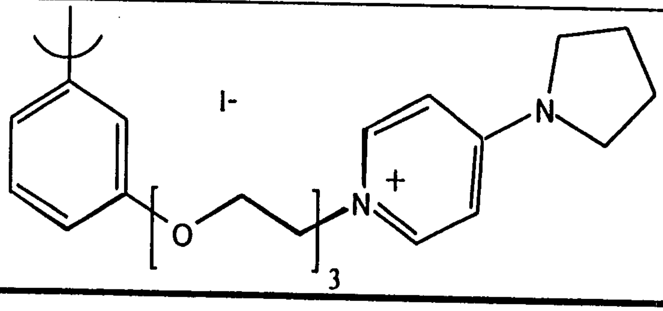
1092	n-butyl	n-butyl	OH	H	
1093	n-butyl	n-butyl	OH	H	

10068297.020802

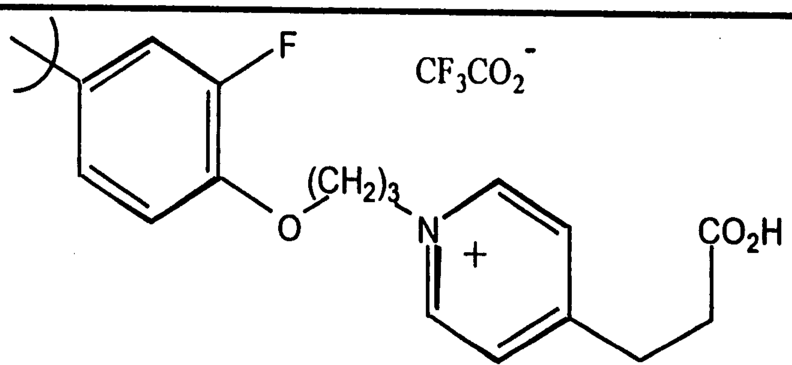
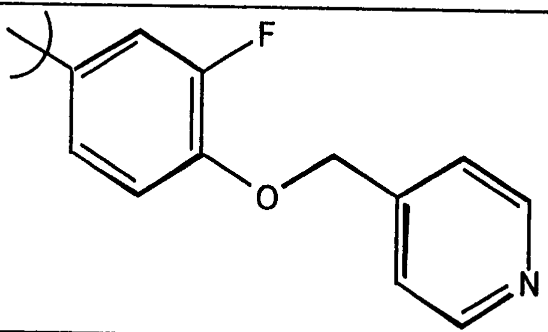
1094	n-butyl	n-butyl	OH	H	
1095	n-butyl	n-butyl	OH	H	

1096	n-butyl	n-butyl	OH	H	
1097	n-butyl	n-butyl	OH	H	
1098	n-butyl	n-butyl	OH	H	 F O 2 S + N(CH2CH3)3 I-
1099	ethyl	n-butyl	OH	H	4-methoxyphenyl
1100	n-butyl	n-butyl	OH	H	4-methoxyphenyl

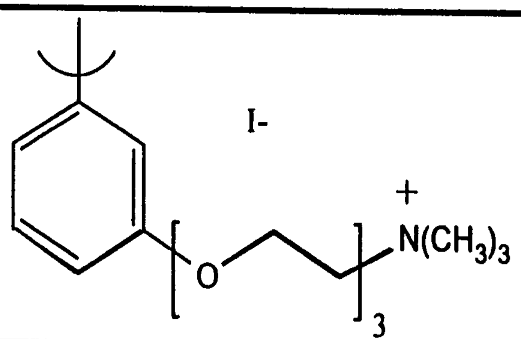
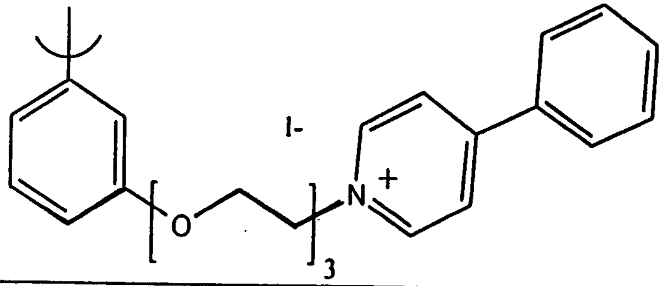
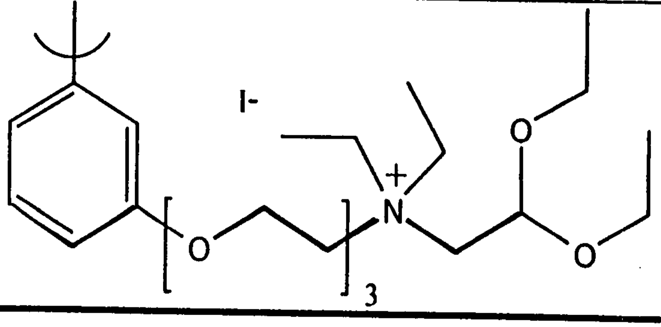
1101	n-butyl	n-butyl	OH	H	 CF$_3$CO$_2^-$
1102	n-butyl	n-butyl	OH	H	3-carboxymethylphenyl
1103	n-butyl	n-butyl	OH	H	 I- I-
1104	n-butyl	n-butyl	OH	H	 I-
1105	n-butyl	n-butyl	OH	H	5-piperonyl
1106	n-butyl	n-butyl	OH	H	3-hydroxyphenyl

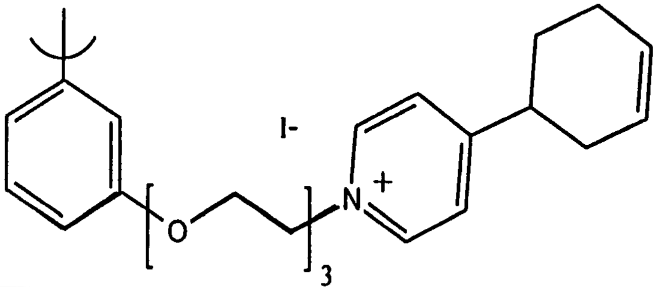
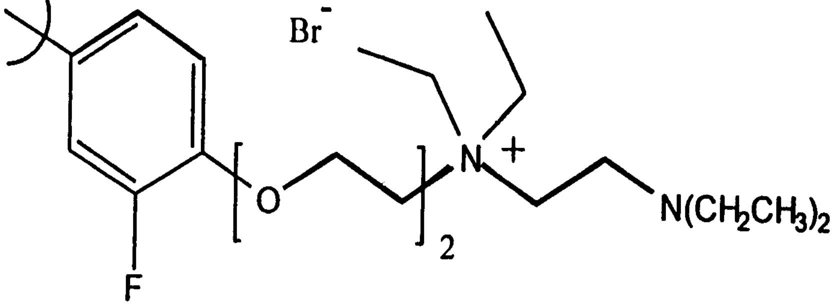
1107	n-butyl	n-butyl	OH	H	
1108	n-butyl	n-butyl	OH	H	3-pyridyl
1109	n-butyl	n-butyl	OH	H	
1110	n-butyl	n-butyl	OH	H	

10068297.020802

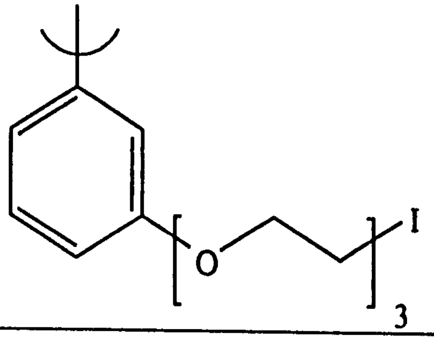
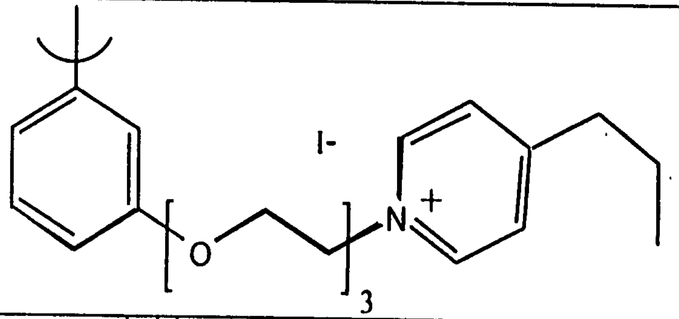
1111	n-butyl	n-butyl	OH	H	 CF$_3$CO$_2^-$
1112	n-butyl	n-butyl	OH	H	4-pyridyl
1113	n-butyl	n-butyl	OH	H	
1114	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1115	n-butyl	n-butyl	OH	H	4-fluorophenyl
1116	ethyl	n-butyl	OH	H	3-tolyl

10068297.020802

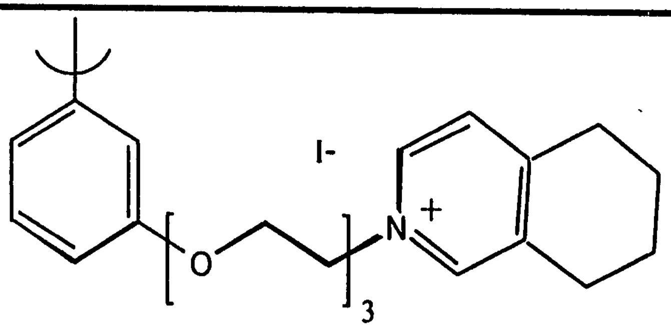
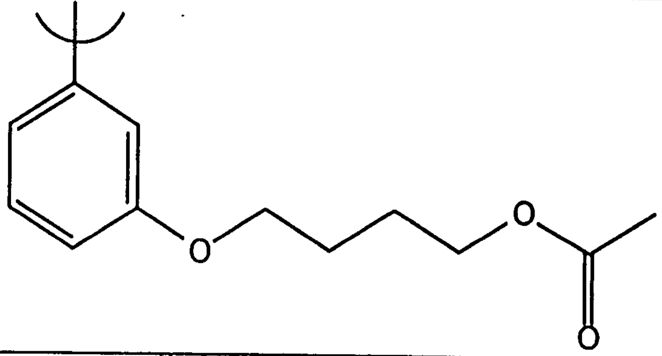
I117	ethyl	n-butyl	OH	H	
I118	ethyl	n-butyl	OH	H	3-fluoro-4-hydroxyphenyl
I119	n-butyl	n-butyl	OH	H	
I120	n-butyl	n-butyl	OH	H	

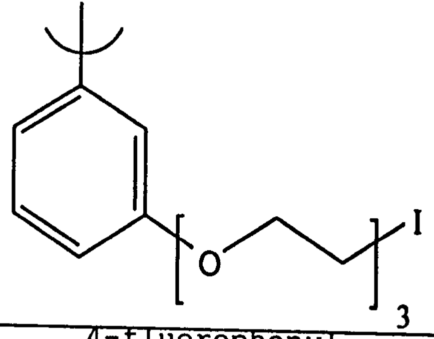
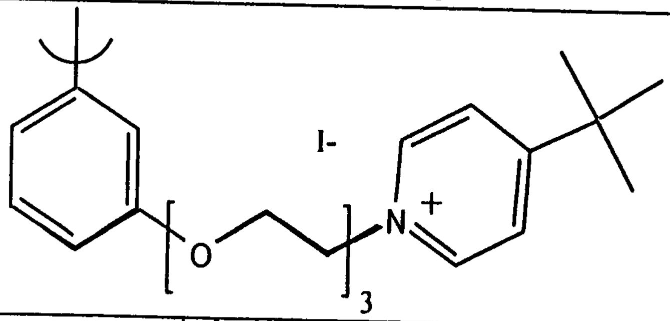
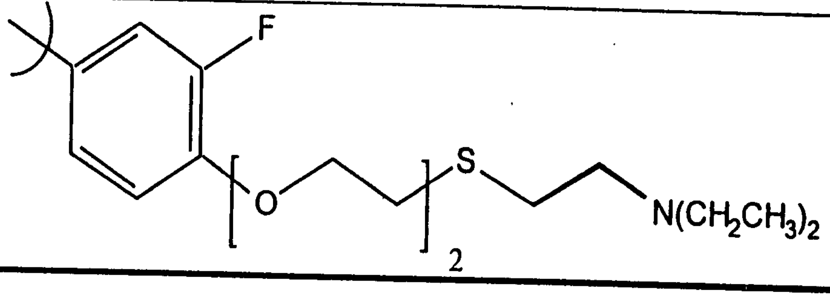
1121	n-butyl	n-butyl	OH	H	
1122	n-butyl	n-butyl	OH	H	
1123	n-butyl	n-butyl	OH	H	phenyl
1124	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1125	n-butyl	n-butyl	OH	H	3-chloro-4-methoxyphenyl

10068297.020802

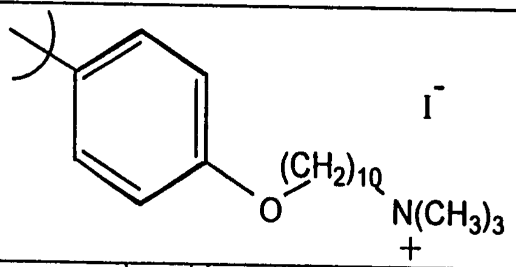
I126	ethyl	n-butyl	OH	H	
I127	n-butyl	n-butyl	OH	H	
I128	n-butyl	n-butyl	OH	H	3-fluoro-4-hydroxyphenyl
I129	n-butyl	n-butyl	OH	H	4-fluorophenyl
I130	n-butyl	n-butyl	OH	H	3-chloro-4-fluorophenyl
I131	ethyl	n-butyl	OH	H	4-methoxyphenyl

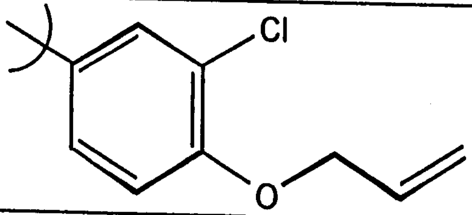
10068297.020802

1132	n-butyl	n-butyl	OH	H	
1133	n-butyl	n-butyl	OH	H	4-cyanomethylphenyl
1134	ethyl	n-butyl	OH	H	
1135	n-butyl	n-butyl	OH	H	3,4-dimethoxyphenyl

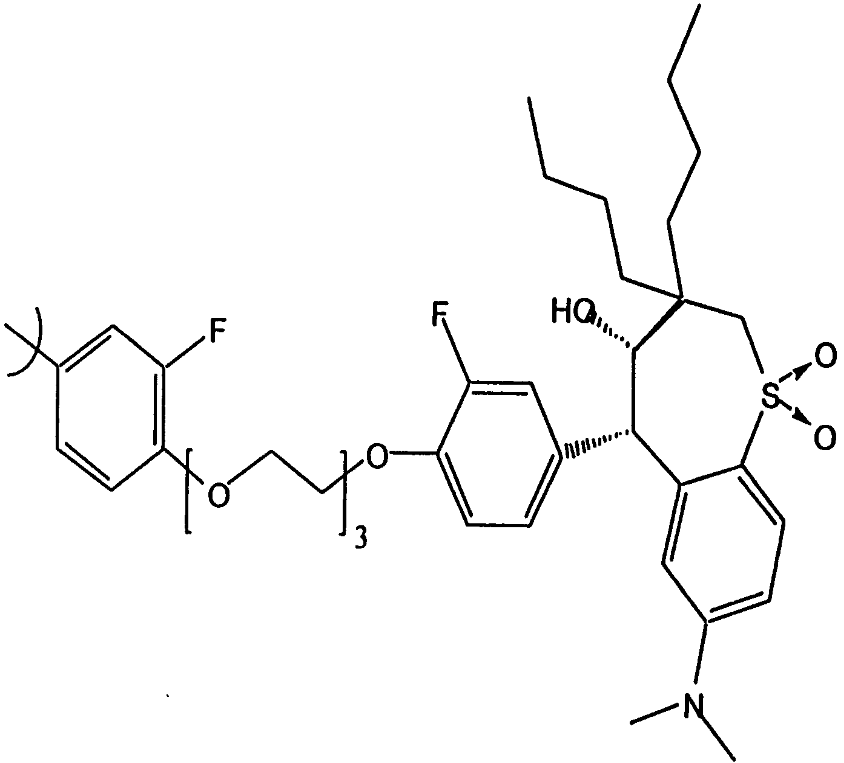
1136	n-butyl	n-butyl	OH	H	
1137	n-butyl	n-butyl	OH	H	4-fluorophenyl
1138	n-butyl	n-butyl	OH	H	
1139	n-butyl	n-butyl	OH	H	3,4-difluorophenyl
1140	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1141	n-butyl	n-butyl	OH	H	4-fluorophenyl
1142	n-butyl	n-butyl	OH	H	

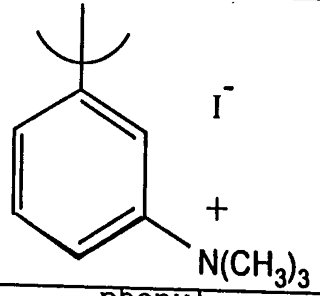
10068297.020802

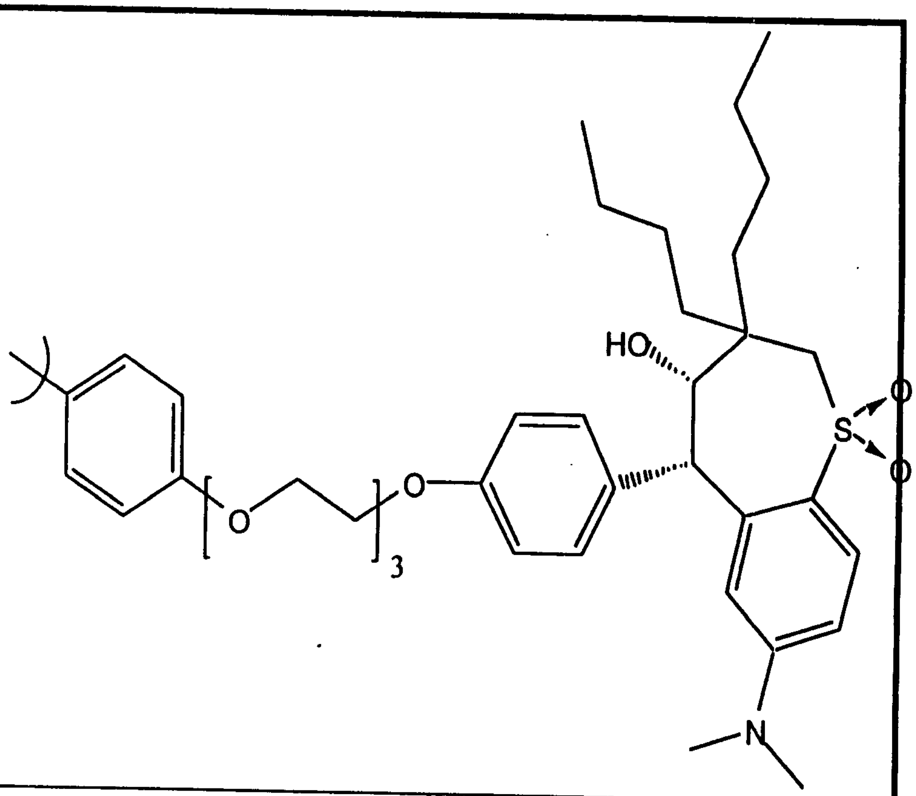
I143	n-butyl	n-butyl	H	OH	H
I144	n-butyl	n-butyl	OH	H	5-piperonyl
I145	n-butyl	n-butyl	OH	H	4-methoxyphenyl
I146	n-butyl	n-butyl	OH	H	
I147	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I148	n-butyl	n-butyl	OH	H	4-fluorophenyl
I149	n-butyl	n-butyl	OH	H	4-fluorophenyl
I150	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I151	n-butyl	ethyl	OH	H	3-fluoro-4-methoxyphenyl
I152	n-butyl	n-butyl	OH	H	phenyl
I153	n-butyl	n-butyl	OH	H	4-fluorophenyl
I154	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I155	n-butyl	n-butyl	OH	H	4-fluorophenyl
I156	n-butyl	n-butyl	OH	H	4-fluorophenyl
I157	n-butyl	n-butyl	OH	H	4-fluorophenyl
I158	n-butyl	n-butyl	OH	H	4-pyridinyl, hydrochloride salt
I159	n-butyl	ethyl	OH	H	phenyl
I160	n-butyl	n-butyl	OH	H	4-fluorophenyl
I161	n-butyl	n-butyl	OH	H	3,5-dichloro-4-methoxyphenyl
I162	n-butyl	n-butyl	OH	H	phenyl
I163	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl
I164	n-butyl	n-butyl	OH	H	4-pyridinyl
I165	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl

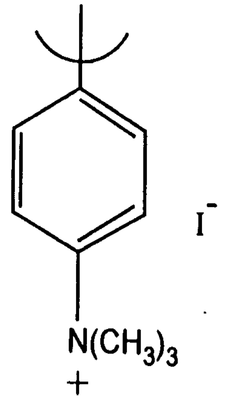
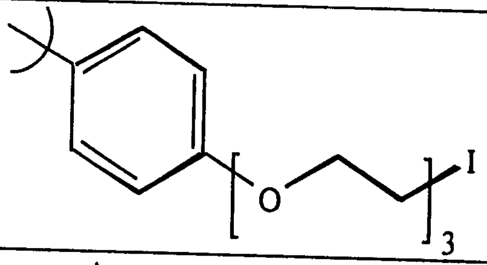
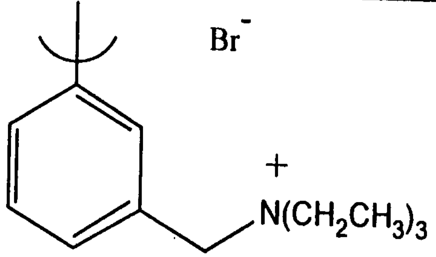
I166	n-butyl	n-butyl	OH	H	3-hydroxyphenyl
I167	n-butyl	n-butyl	OH	H	
I168	n-butyl	n-butyl	OH	H	4-hydroxyphenyl
I169	n-butyl	n-butyl	OH	H	phenyl
I170	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I171	n-butyl	n-butyl	OH	H	4-(trifluoromethylsulfonyloxy)phenyl
I172	n-butyl	n-butyl	OH	H	4-pyridinyl
I173	n-butyl	n-butyl	OH	H	4-fluorophenyl
I174	ethyl	n-butyl	OH	H	3-methoxyphenyl
I175	ethyl	n-butyl	OH	H	3-methoxyphenyl
I176	n-butyl	n-butyl	OH	H	4-fluorophenyl
I177	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I178	n-butyl	n-butyl	OH	H	3-(trifluoromethylsulfonyloxy)phenyl
I179	n-butyl	n-butyl	OH	H	phenyl
I180	n-butyl	n-butyl	OH	H	phenyl
I181	n-butyl	n-butyl	OH	H	4-fluorophenyl
I182	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl
I183	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I184	n-butyl	n-butyl	OH	H	4-fluorophenyl
I185	n-butyl	n-butyl	OH	H	4-fluorophenyl
I186	n-butyl	n-butyl	OH	H	phenyl
I187	n-butyl	n-butyl	OH	H	4-fluorophenyl
I188	n-butyl	n-butyl	OH	H	4-methoxyphenyl
I189	n-butyl	n-butyl	OH	H	3,4-difluorophenyl

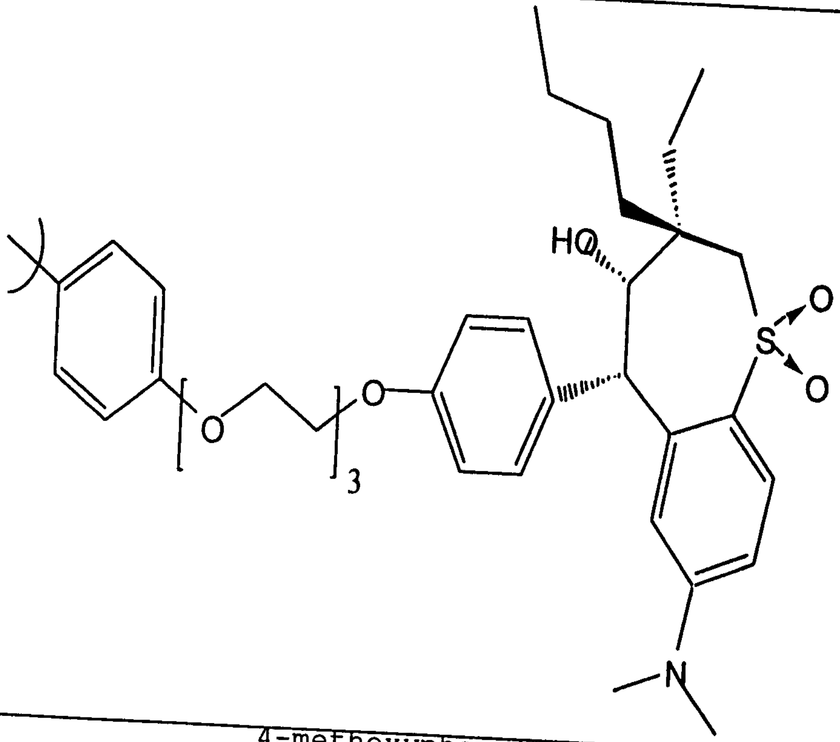
10068297.020802

I190	n-butyl	n-butyl	OH	H	2-bromophenyl
I191	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl
I192	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl
I193	n-butyl	n-butyl	OH	H	4-(2-(2-methylpropyl))phenyl
I194	n-butyl	n-butyl	OH	H	
I195	n-butyl	n-butyl	OH	H	4-methoxyphenyl

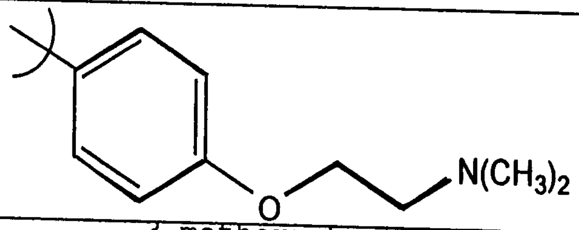
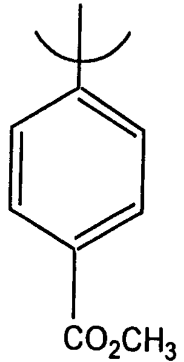
1196	n-butyl	n-butyl	OH	H	
1197	n-butyl	ethyl	R3 + R4 = oxo	R3 + R4 = oxo	phenyl
1198	n-butyl	n-butyl	OH	H	4-(pyridinyl-N-oxide)

1199	n-butyl	n-butyl	OH	H	
1200	n-butyl	n-butyl	H	OH	H
1201	n-butyl	n-butyl	OH	H	H

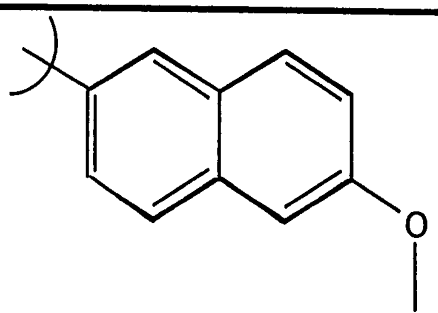
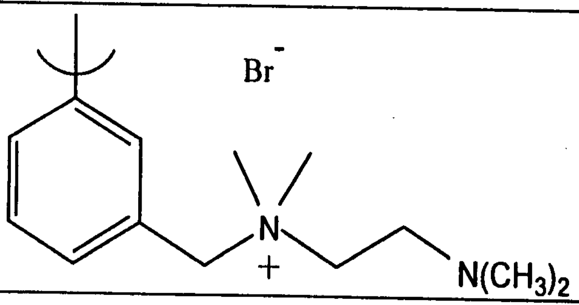
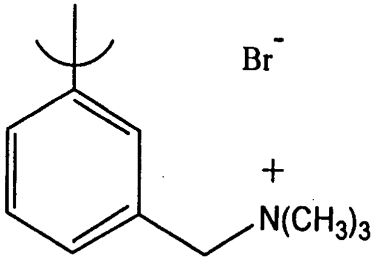
I202	n-butyl	n-butyl	OH	H	
I203	n-butyl	n-butyl	OH	H	5-piperazinyl
I204	n-butyl	n-butyl	OH	H	4-fluorophenyl
I205	n-butyl	n-butyl	OH	H	
I206	n-butyl	n-butyl	OH	H	
I207	n-butyl	n-butyl	OH	H	3,5-dichlorophenyl

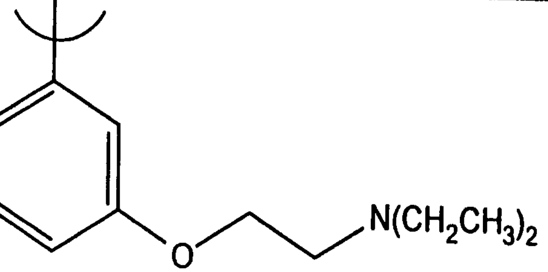
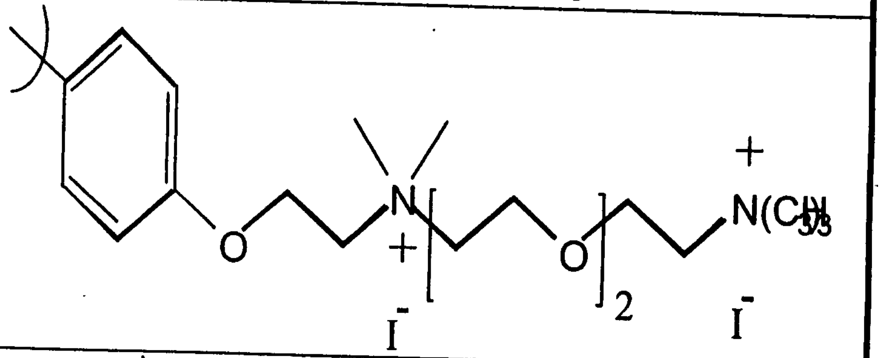
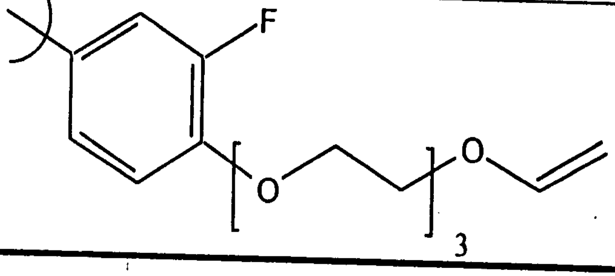
I208	n-butyl	n-butyl	OH	H	4-methoxyphenyl
I209	n-butyl	n-butyl	acetoxy	H	phenyl
I210	n-butyl	n-butyl	OH	H	2-(dimethylamino)phenyl
I211	ethyl	n-butyl	OH	H	
I212	n-butyl	n-butyl	OH	H	4-methoxyphenyl
I213	n-butyl	ethyl	H	OH	H
I214	n-butyl	ethyl	OH	H	phenyl
I215	n-butyl	n-butyl	OH	H	4-methoxyphenyl

10068297.020802

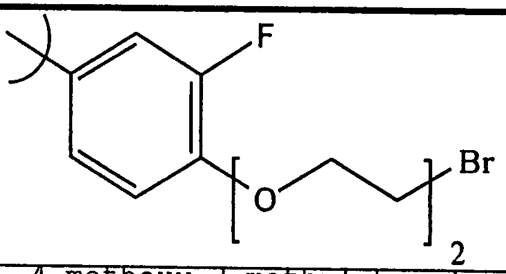
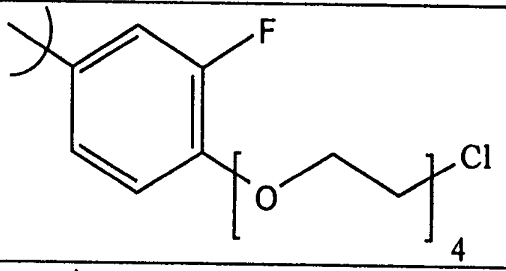
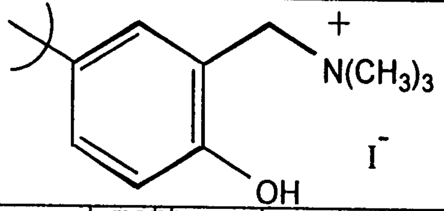
I216	ethyl	n-butyl	OH	H	5-piperonyl
I217	n-butyl	n-butyl	OH	H	4-carboxyphenyl
I218	n-butyl	n-butyl	OH	H	4-methoxyphenyl
I219	n-butyl	n-butyl	OH	H	
I220	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I221	n-butyl	n-butyl	OH	H	
I222	n-butyl	n-butyl	OH	H	3-methoxyphenyl
I223	n-butyl	n-butyl	OH	H	phenyl
I224	n-butyl	n-butyl	OH	H	3-nitrophenyl
I225	n-butyl	ethyl	OH	H	3-methylphenyl
I226	ethyl	n-butyl	OH	H	5-piperonyl
I227	n-butyl	n-butyl	OH	H	4-fluorophenyl
I228	n-butyl	n-butyl	OH	H	2-pyrrolyl
I229	n-butyl	n-butyl	OH	H	3-chloro-4-hydroxyphenyl
I230	n-butyl	n-butyl	OH	H	phenyl

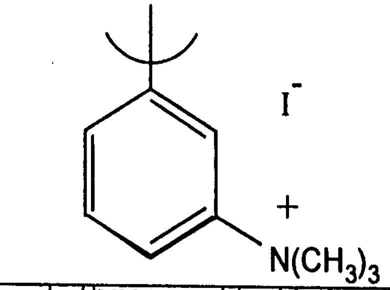
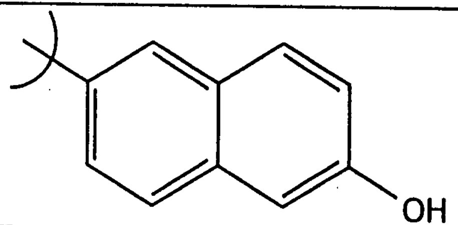
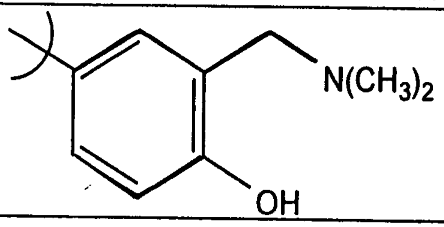
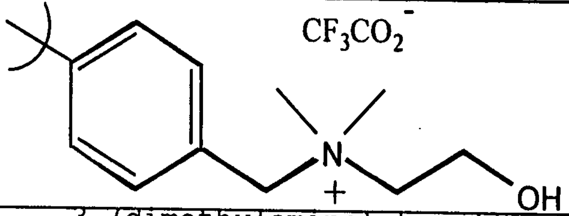
10068297.020802

1231	n-butyl	n-butyl	OH	H	
1232	n-butyl	n-butyl	H	OH	3-thiophenyl
1233	n-butyl	n-butyl	OH	H	
1234	n-butyl	n-butyl	OH	H	

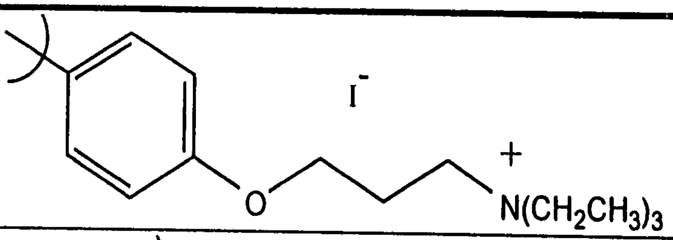
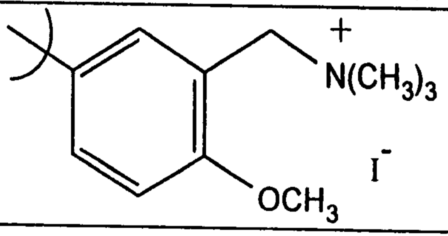
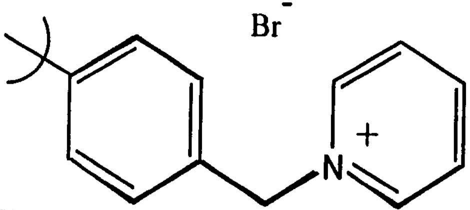
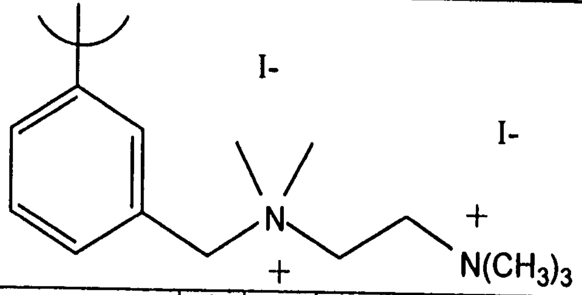
I235	n-butyl	n-butyl	OH	H	
I236	n-butyl	n-butyl	OH	H	4-(bromomethyl)phenyl
I237	n-butyl	n-butyl	OH	H	
I238	n-butyl	n-butyl	OH	H	

10068297 .020802

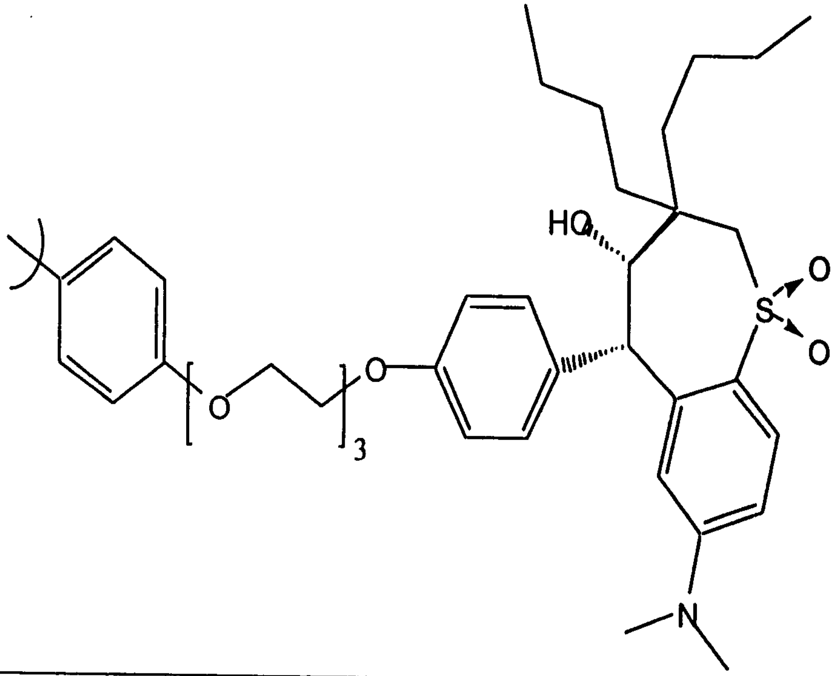
1239	n-butyl	n-butyl	OH	H	
1240	n-butyl	n-butyl	OH	H	4-methoxy-3-methylphenyl
1241	n-butyl	n-butyl	OH	H	3-(dimethylaminomethyl)phenyl
1242	n-butyl	n-butyl	OH	H	
1243	n-butyl	n-butyl	OH	H	
1244	n-butyl	n-butyl	OH	H	3-methoxyphenyl

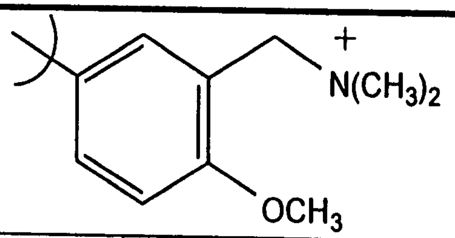
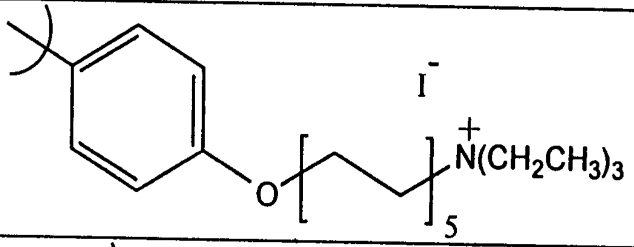
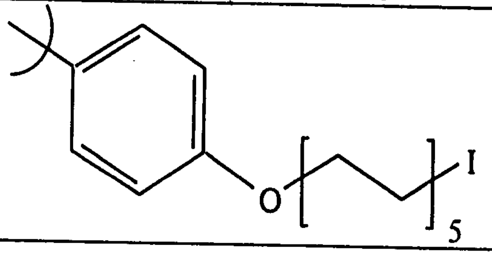
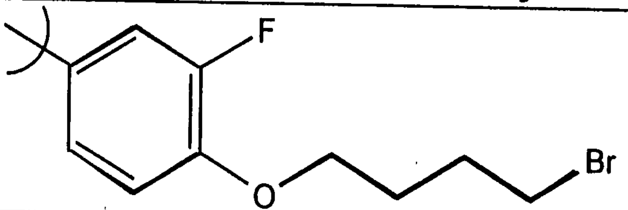
1245	n-butyl	n-butyl	OH	H	
1246	n-butyl	n-butyl	OH	H	3-(bromomethyl)phenyl
1247	n-butyl	n-butyl	OH	H	
1248	n-butyl	n-butyl	OH	H	
1249	n-butyl	n-butyl	OH	H	
1250	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl
1251	n-butyl	n-butyl	OH	H	1-naphthyl

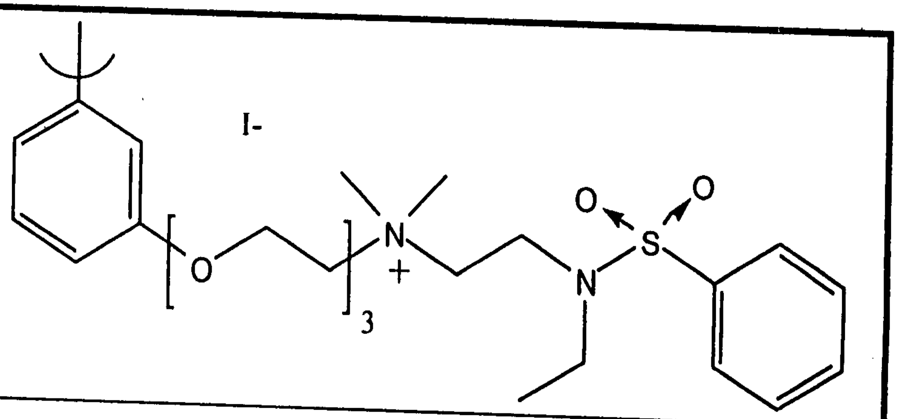
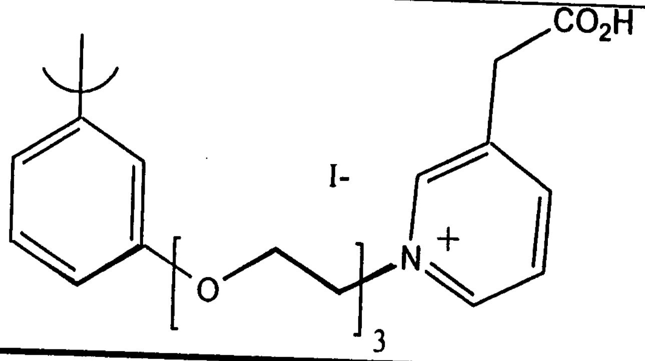
10068297.020802

I252	n-butyl	n-butyl	OH	H	
I253	n-butyl	n-butyl	OH	H	
I254	n-butyl	n-butyl	OH	H	
I255	n-butyl	n-butyl	OH	H	
I256	n-butyl	n-butyl	OH	H	3-nitrophenyl
I257	n-butyl	n-butyl	OH	H	phenyl

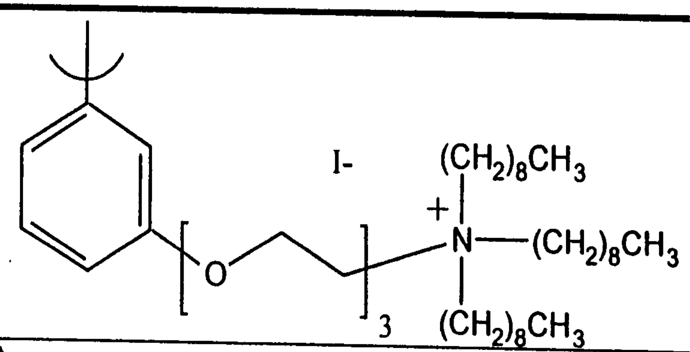
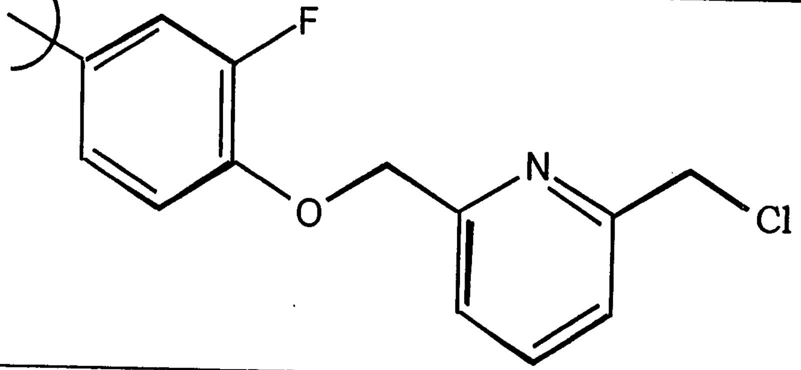
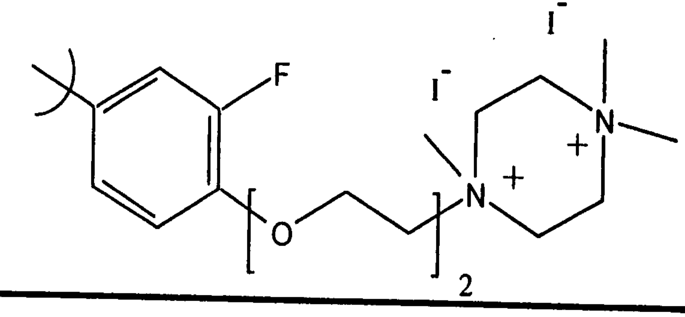
10068297.020802

1258	n-butyl	n-butyl	OH	H	4-fluorophenyl
1259	ethyl	n-butyl	H	OH	H
1260	ethyl	n-butyl	OH	H	3-hydroxyphenyl
1261	n-butyl	n-butyl	OH	H	
1262	n-butyl	n-butyl	OH	H	2-thiophenyl
1263	n-butyl	n-butyl	OH	H	5-piperonyl
1264	n-butyl	n-butyl	OH	H	4-fluorophenyl
1265	n-butyl	n-butyl	OH	H	4-fluorophenyl

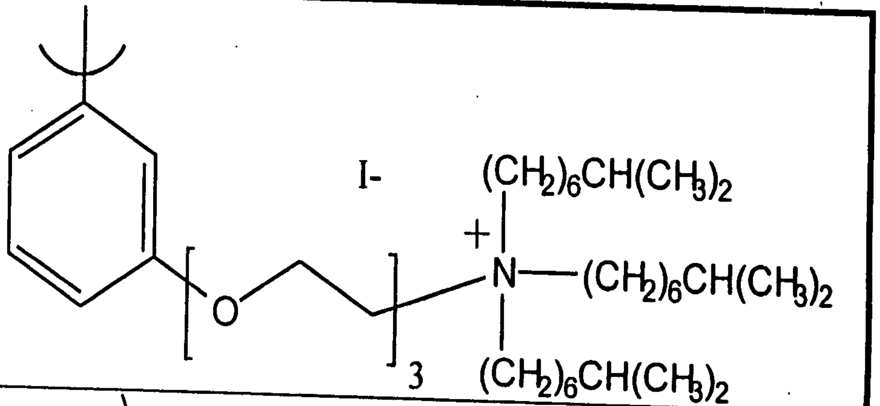
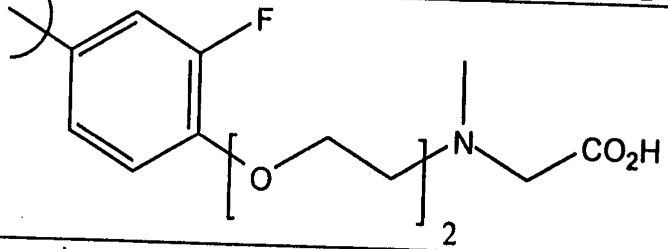
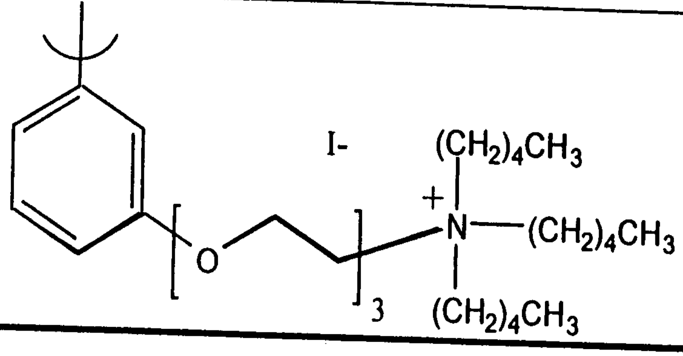
1266	n-butyl	n-butyl	OH	H	
1267	n-butyl	ethyl	OH	H	5-piperonyl
1268	n-butyl	n-butyl	OH	H	
1269	n-butyl	n-butyl	OH	H	
1270	n-butyl	n-butyl	OH	H	

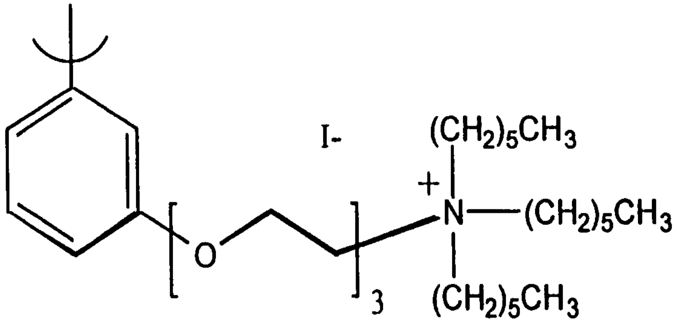
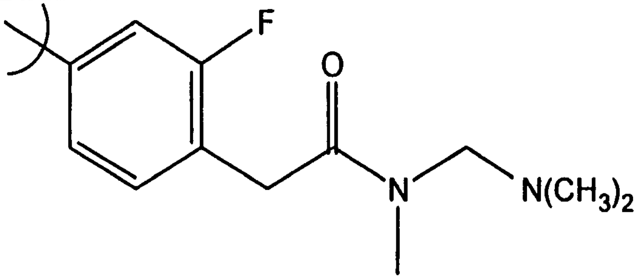
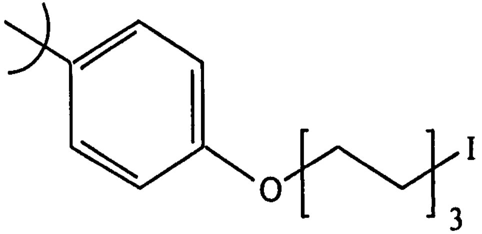
1271	n-butyl	n-butyl	OH	H	
1272	n-butyl	n-butyl	OH	H	

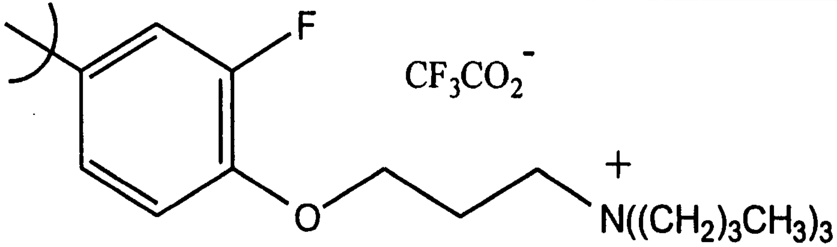
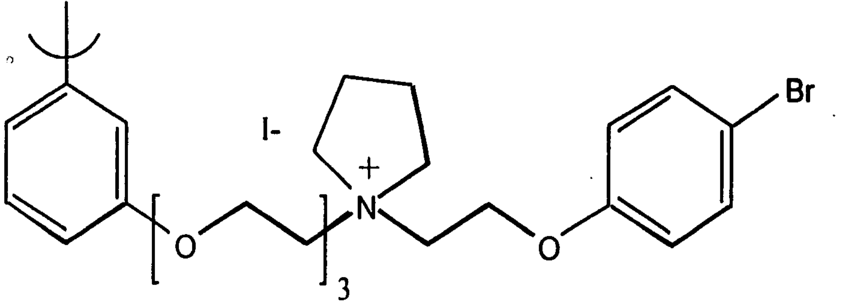
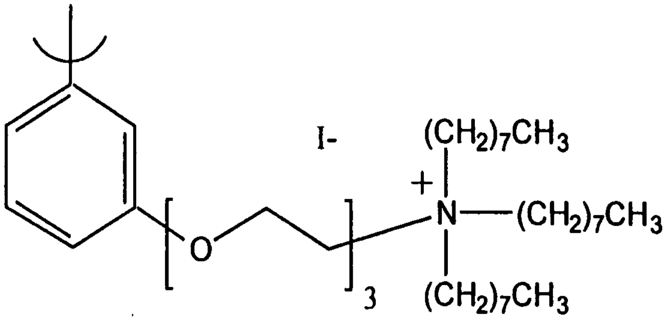
10068297.020802

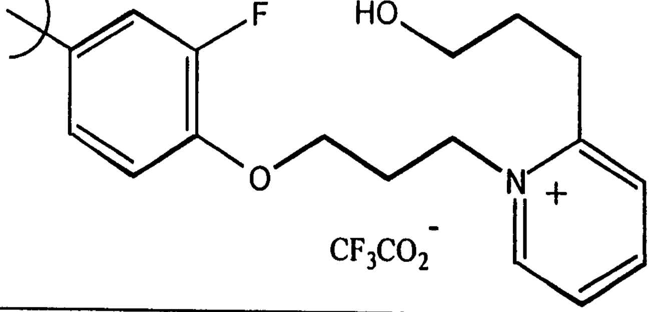
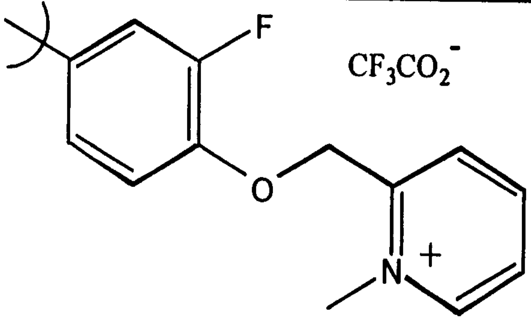
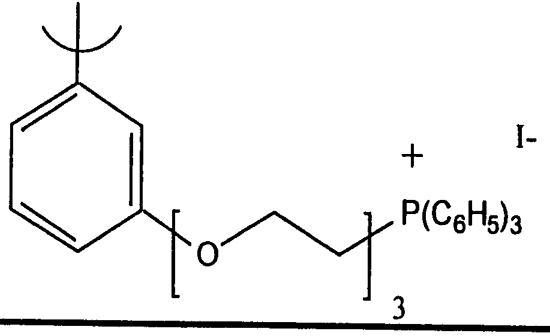
1273	n-butyl	n-butyl	OH	H	 I- + N (CH2)8CH3 (CH2)8CH3 (CH2)8CH3 O 3
1274	n-butyl	n-butyl	OH	H	
1275	n-butyl	n-butyl	OH	H	

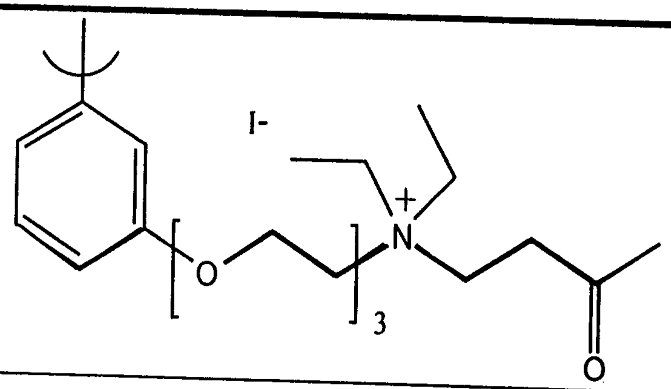
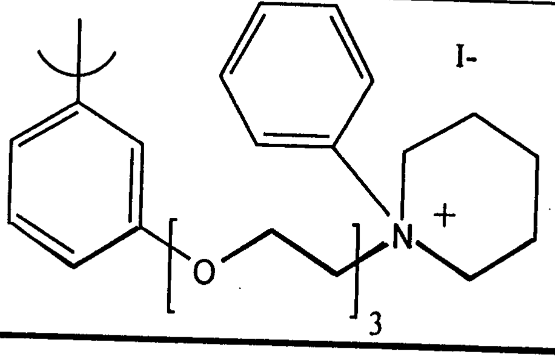
10068297.020802

1276	n-butyl	n-butyl	OH	H	
1277	n-butyl	n-butyl	OH	H	
1278	n-butyl	n-butyl	OH	H	

1279	n-butyl	n-butyl	OH	H	
1280	n-butyl	n-butyl	OH	H	
1281	n-butyl	n-butyl	OH	H	
1282	ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1283	n-butyl	n-butyl	OH	H	4-hydroxymethylphenyl
1284	n-butyl	n-butyl	OH	H	4-fluorophenyl
1285	n-butyl	ethyl	OH	H	phenyl

1286	n-butyl	n-butyl	OH	H	 F $CF_3CO_2^-$ O + $N((CH_2)_3CH_3)_3$
1287	n-butyl	ethyl	OH	H	4-hydroxyphenyl
1288	n-butyl	n-butyl	OH	H	
1289	n-butyl	n-butyl	OH	H	 I- $(CH_2)_7CH_3$ + N $(CH_2)_7CH_3$ $(CH_2)_7CH_3$ O 3

1290	n-butyl	n-butyl	OH	H	 F HO O N+ $CF_3CO_2^-$
1291	n-butyl	n-butyl	OH	H	
1292	n-butyl	n-butyl	OH	H	

I293	n-butyl	n-butyl	OH	H	
I294	n-butyl	n-butyl	OH	H	

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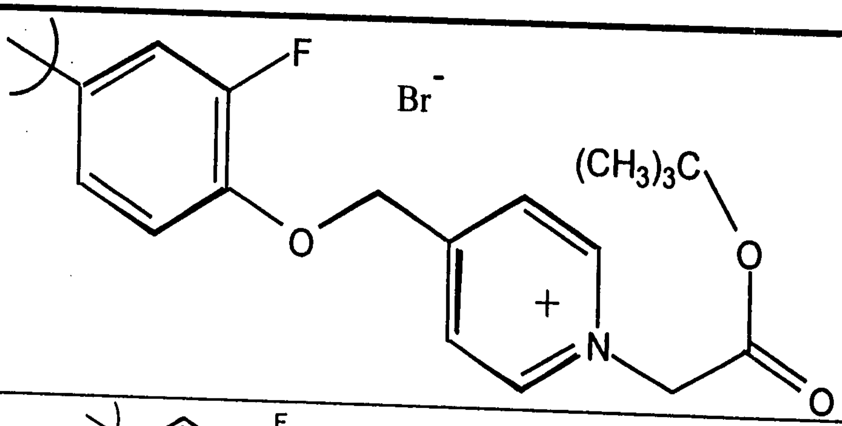
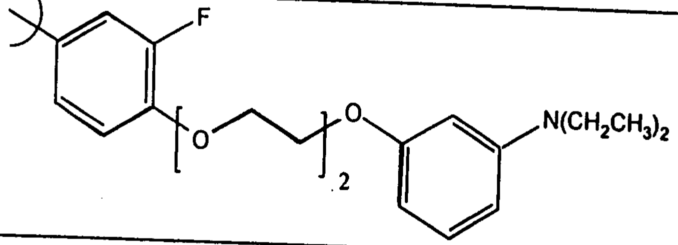
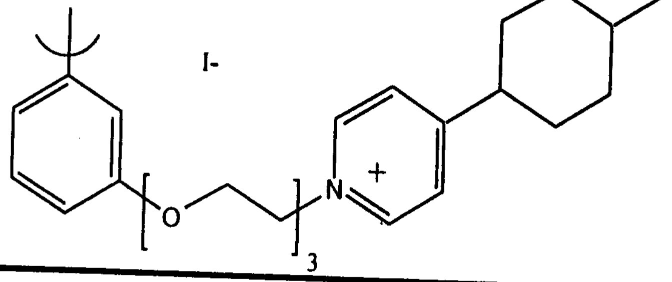
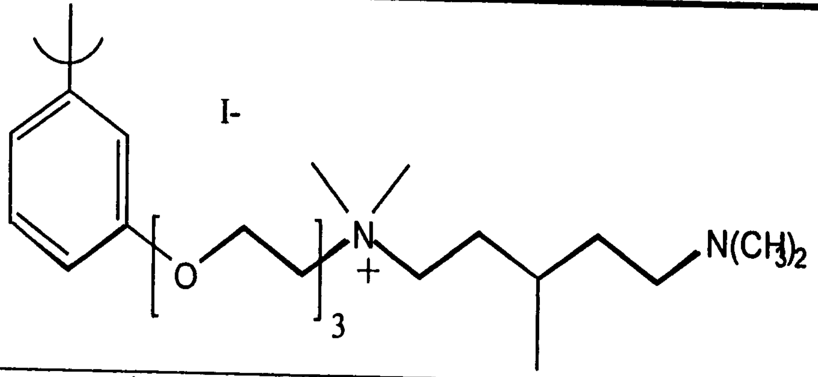
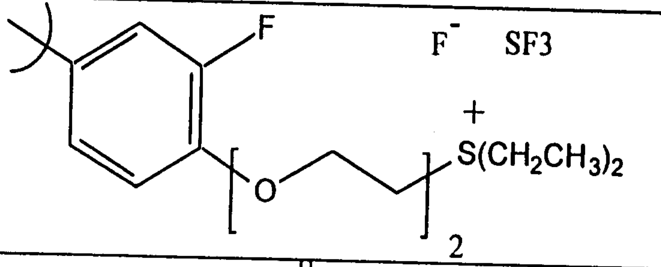
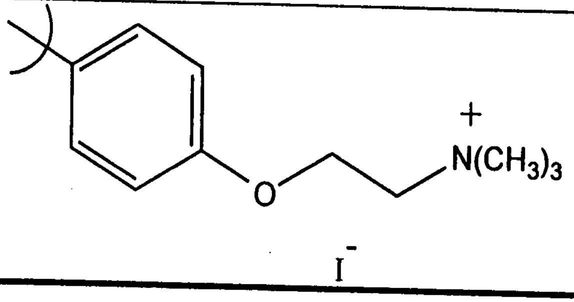
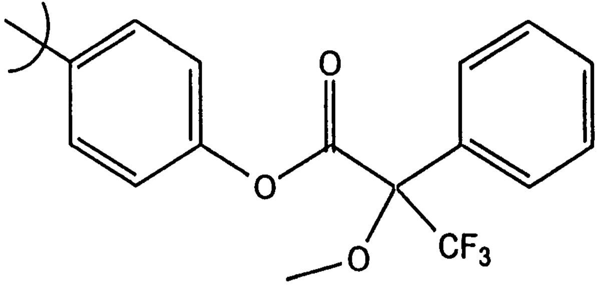
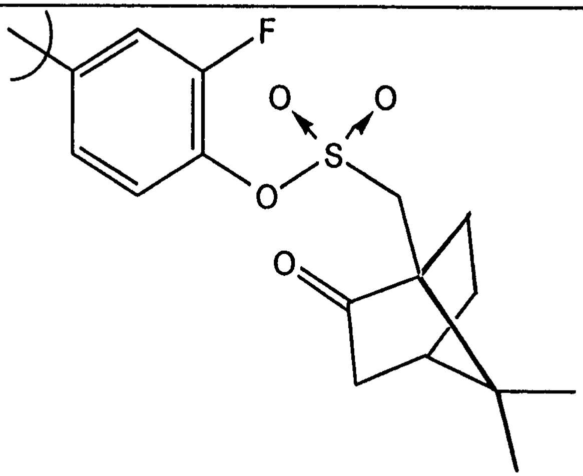
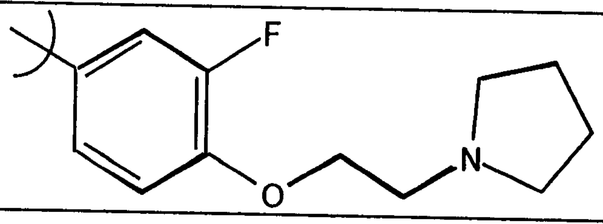
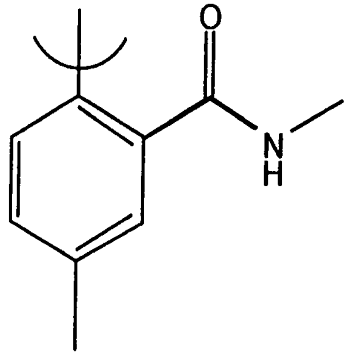
I295	n-butyl	n-butyl	OH	H	
I296	n-butyl	n-butyl	OH	H	
I297	n-butyl	n-butyl	OH	H	

1298	n-butyl	n-butyl	OH	H	
1299	n-butyl	n-butyl	OH	H	
1300	n-butyl	ethyl	H	OH	H
1301	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1302	n-butyl	n-butyl	OH	H	3-hydroxyphenyl
1303	n-butyl	n-butyl	OH	H	

10068297.020602

1304	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1305	n-butyl	n-butyl	OH	H	4-fluorophenyl
1306	n-butyl	n-butyl	OH	H	
1307	n-butyl	n-butyl	OH	H	H
1308	ethyl	n-butyl	OH	H	
1309	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1310	ethyl	n-butyl	OH	H	phenyl
1311	n-butyl	ethyl	OH	H	phenyl
1312	n-butyl	ethyl	OH	H	phenyl

1313	n-butyl	ethyl	OH	H	phenyl
1314	ethyl	n-butyl	OH	H	phenyl
1315	ethyl	n-butyl	OH	H	phenyl
1316	n-butyl	ethyl	OH	H	phenyl
1317	n-butyl	ethyl	OH	H	phenyl
1318	ethyl	n-butyl	OH	H	phenyl
1319	ethyl	n-butyl	OH	H	3-methoxyphenyl
1320	ethyl	n-butyl	OH	H	phenyl
1321	n-butyl	ethyl	OH	H	phenyl
1322	n-butyl	n-butyl	OH	H	
1323	n-butyl	n-butyl	OH	H	

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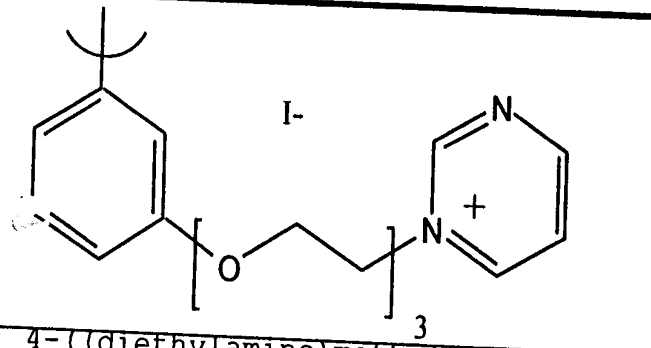
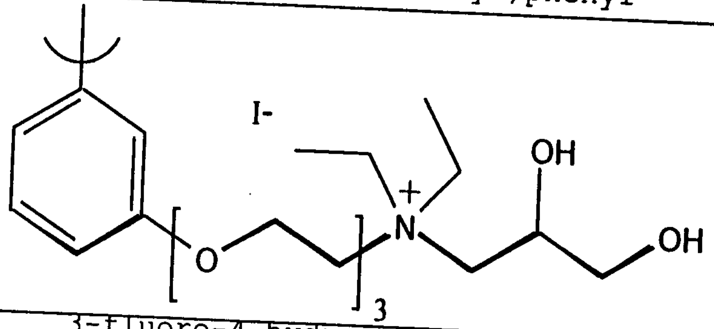
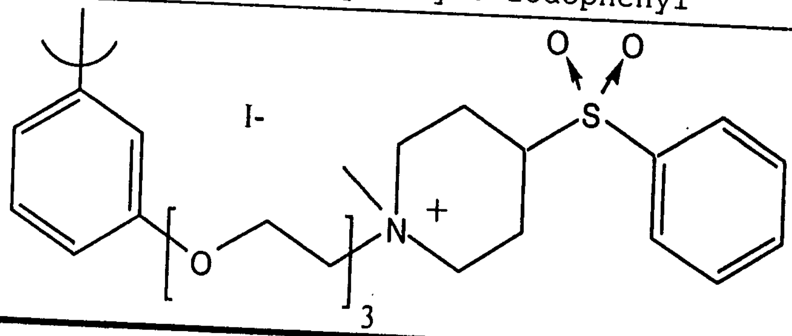
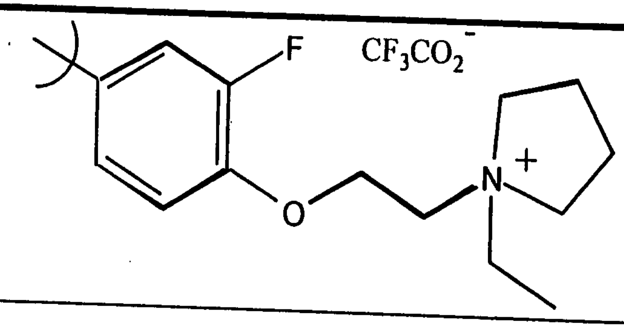
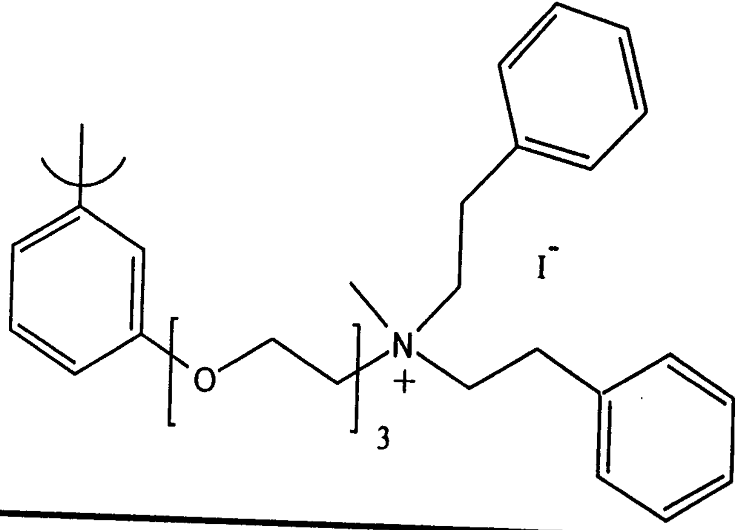
1324	n-butyl	n-butyl	OH	H	
1325	n-butyl	n-butyl	OH	H	4-((diethylamino)methyl)phenyl
1326	n-butyl	n-butyl	OH	H	
1327	n-butyl	n-butyl	OH	H	3-fluoro-4-hydroxy-5-iodophenyl
1328	n-butyl	n-butyl	OH	H	

1329	n-butyl	n-butyl	OH	H	
1330	n-butyl	n-butyl	OH	H	

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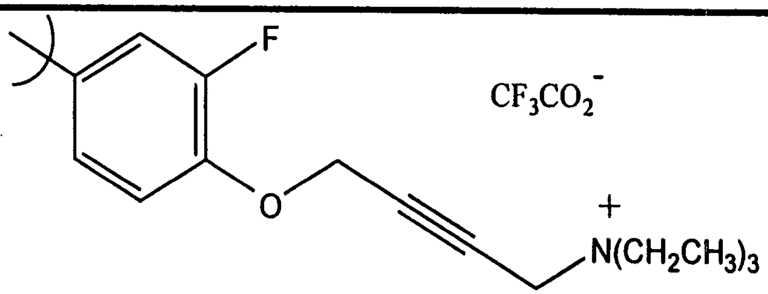
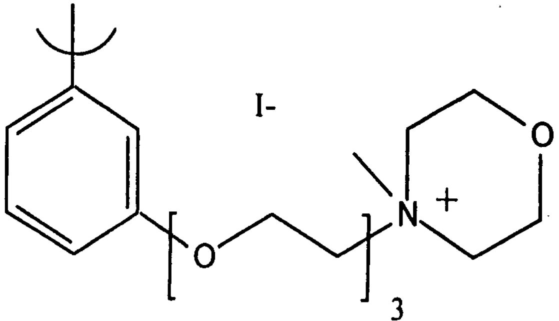
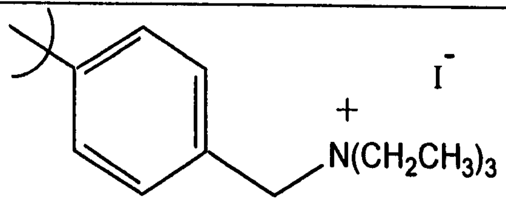
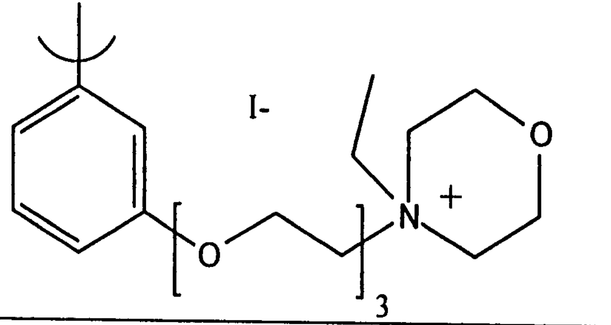
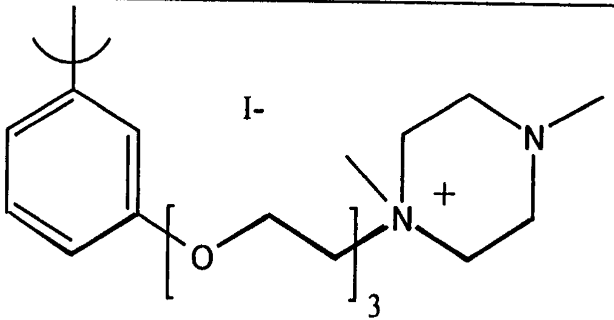
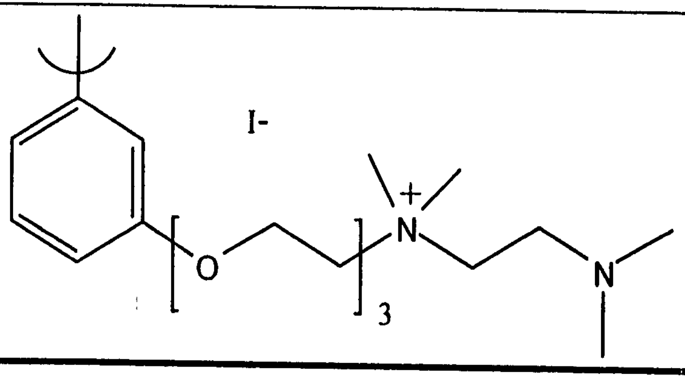
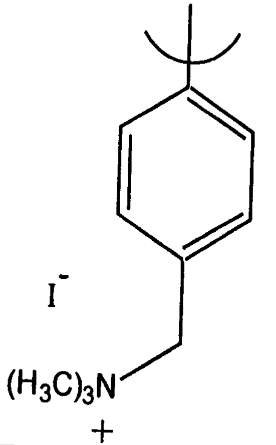
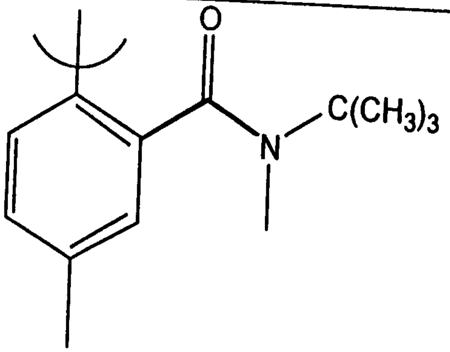
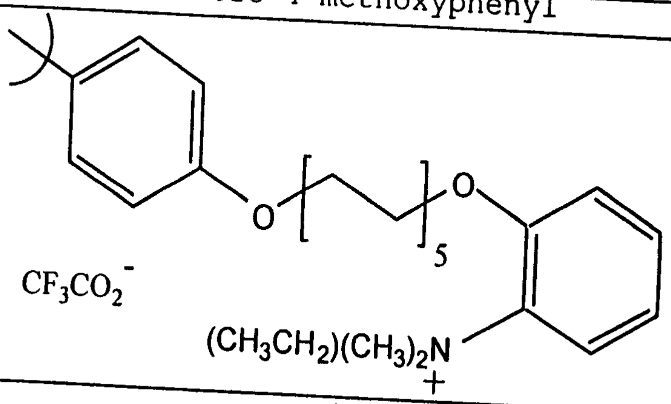
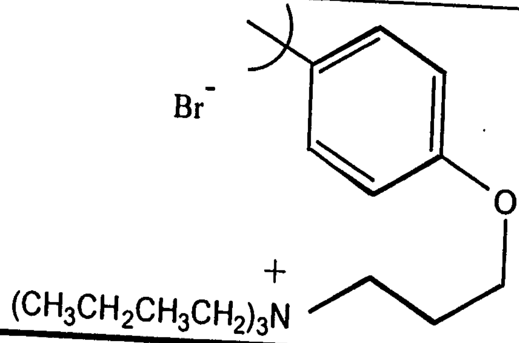
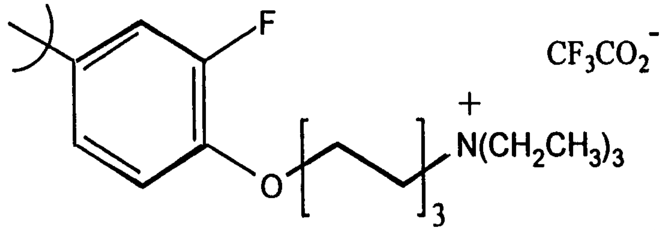
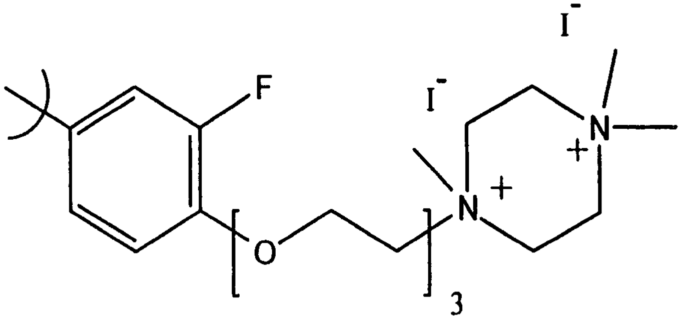
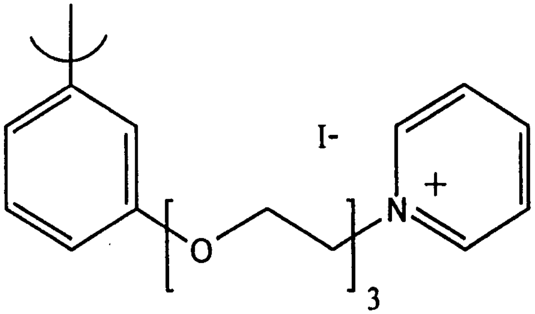
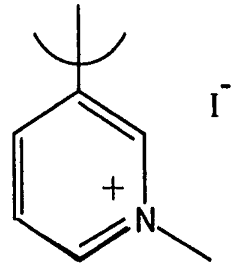
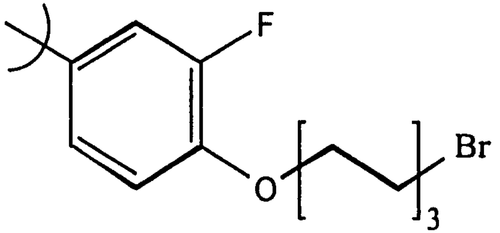
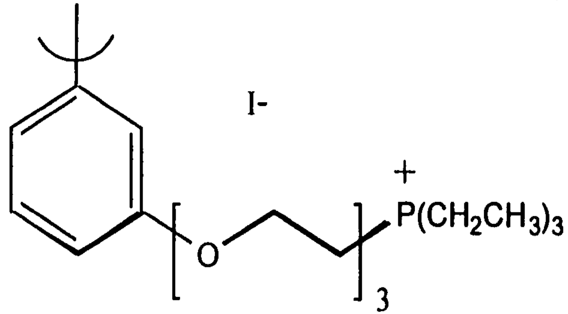
1331	n-butyl	n-butyl	OH	H	 F O CF$_3$CO$_2^-$ + N(CH$_2$CH$_3$)$_3$
1332	n-butyl	n-butyl	OH	H	
1333	n-butyl	n-butyl	OH	H	

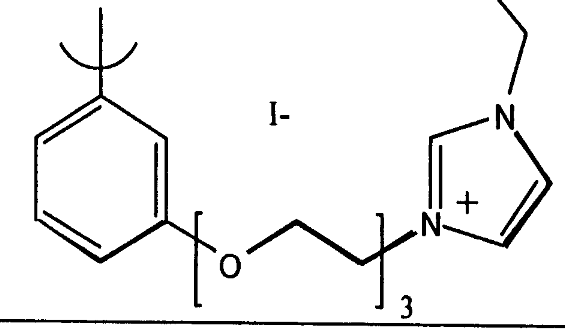
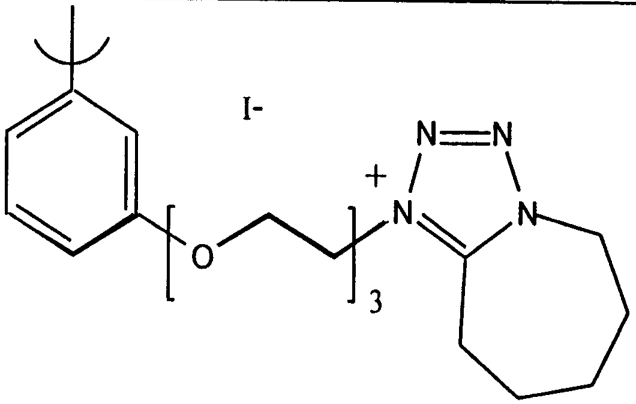
1334	n-butyl	n-butyl	OH	H	
1335	n-butyl	n-butyl	OH	H	
1336	n-butyl	n-butyl	OH	H	

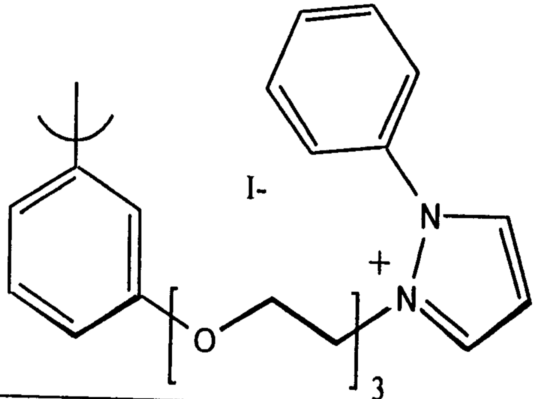
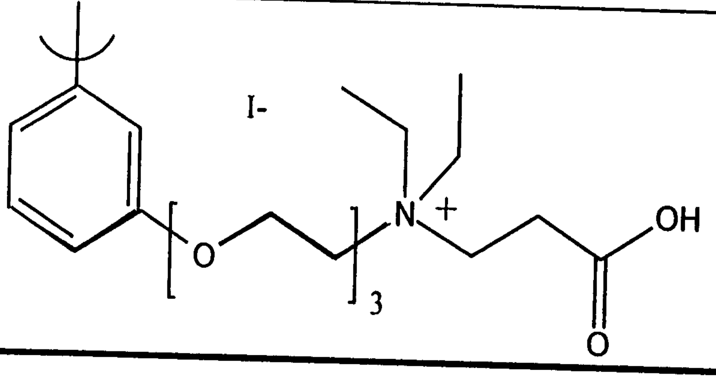
1337	n-butyl	n-butyl	OH	H	
1338	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1339	n-butyl	n-butyl	OH	H	
1340	n-butyl	ethyl	OH	H	5-piperonyl
1341	n-butyl	n-butyl	acetoxy	H	3-methoxyphenyl
1342	n-butyl	n-butyl	OH	H	5-piperonyl
1343	ethyl	n-butyl	OH	H	phenyl

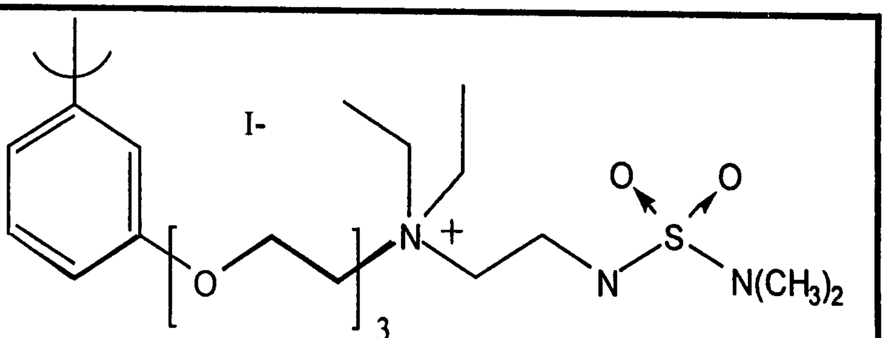
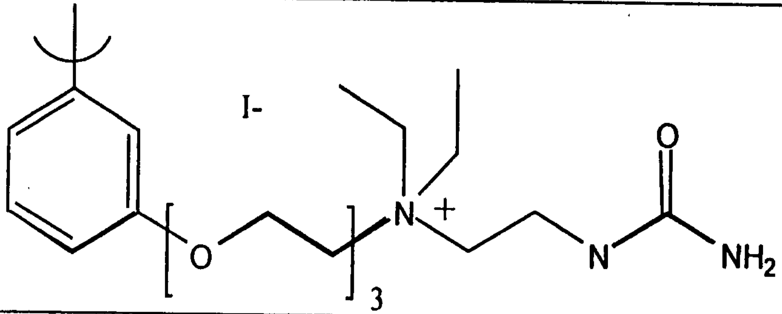
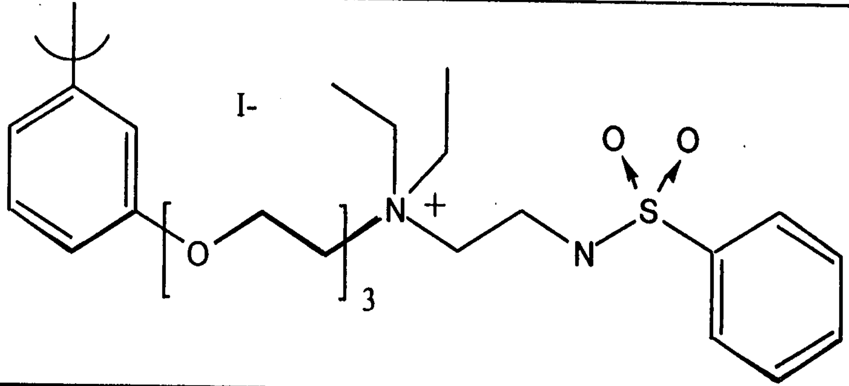
1344	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1345	ethyl	n-butyl	OH	H	phenyl
1346	ethyl	n-butyl	OH	H	phenyl
1347	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1348	isobutyl	isobutyl	OH	H	phenyl
1349	ethyl	n-butyl	OH	H	phenyl
1350	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1351	n-butyl	n-butyl	OH	H	 O O 5 $CF_3CO_2^-$ $(CH_3CH_2)(CH_3)_2N^+$
1352	n-butyl	n-butyl	OH	H	 Br^- O $(CH_3CH_2CH_3CH_2)_3N^+$

1353	n-butyl	n-butyl	OH	H	
1354	n-butyl	n-butyl	OH	H	
1355	n-butyl	n-butyl	OH	H	

1356	n-butyl	n-butyl	OH	H	
1357	n-butyl	n-butyl	OH	H	
1358	n-butyl	n-butyl	OH	H	

1359	n-butyl	n-butyl	OH	H	
1360	n-butyl	n-butyl	OH	H	

1361	n-butyl	n-butyl	OH	H	
1362	n-butyl	n-butyl	OH	H	

1363	n-butyl	n-butyl	OH	H	
1364	n-butyl	n-butyl	OH	H	
1365	n-butyl	n-butyl	OH	H	

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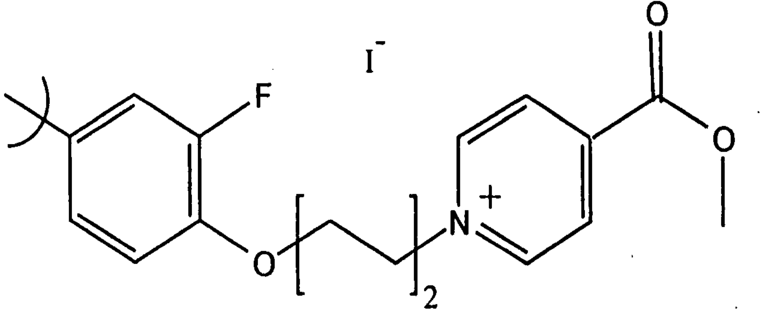
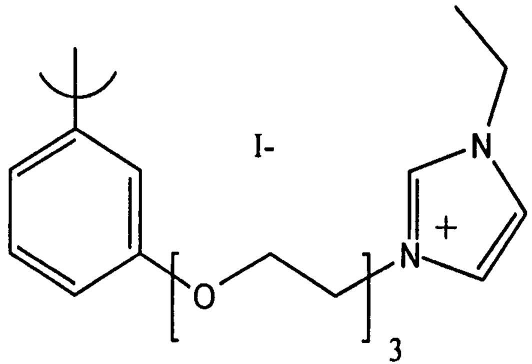
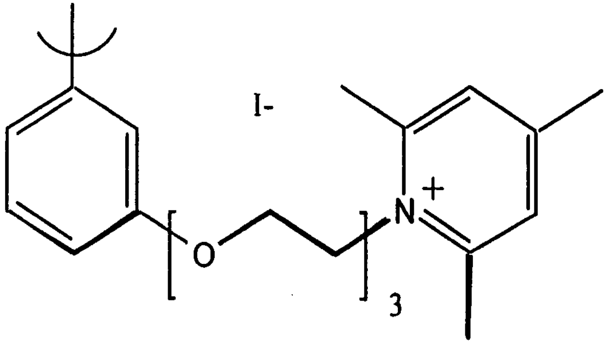
1366	n-butyl	n-butyl	OH	H	
1367	n-butyl	n-butyl	OH	H	
1368	n-butyl	n-butyl	OH	H	

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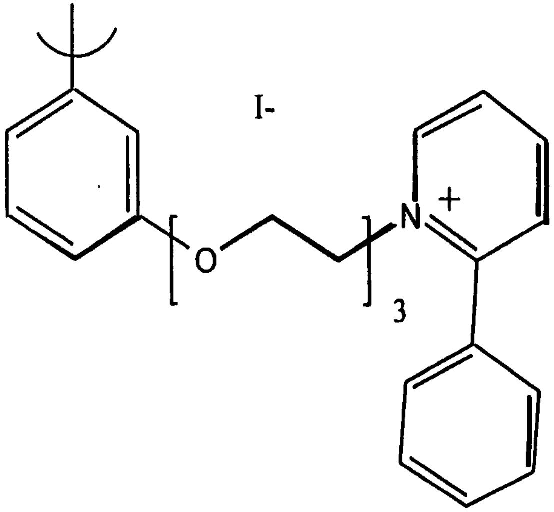
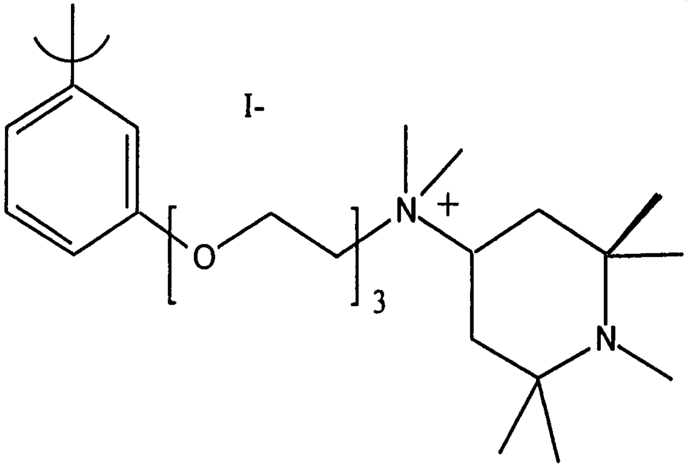
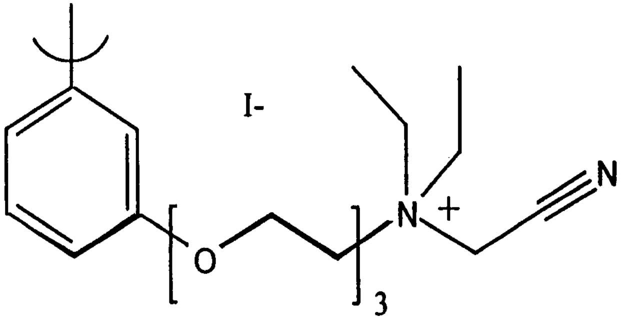
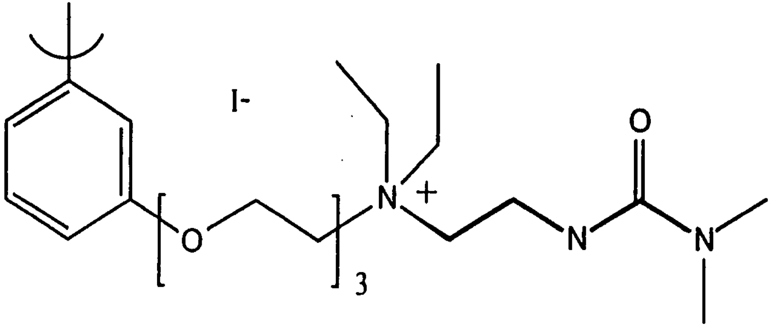
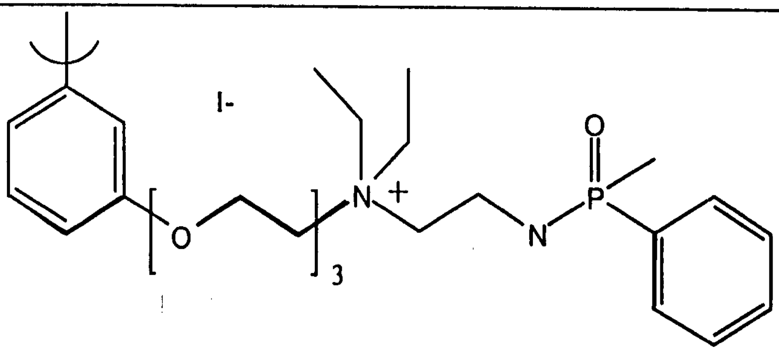
1369	n-butyl	n-butyl	OH	H	
1370	n-butyl	n-butyl	OH	H	

1371	n-butyl	n-butyl	OH	H	
1372	n-butyl	n-butyl	OH	H	
1373	n-butyl	n-butyl	OH	H	

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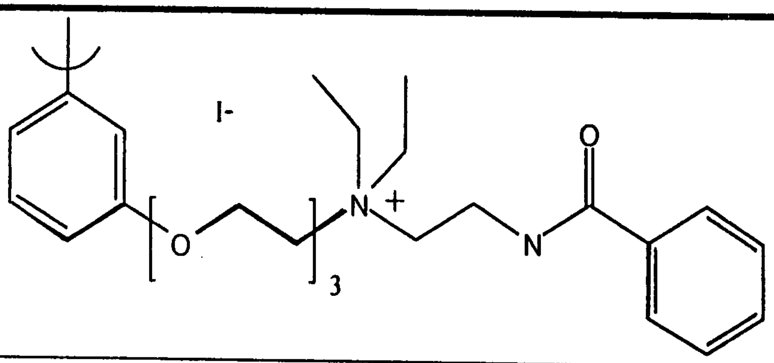
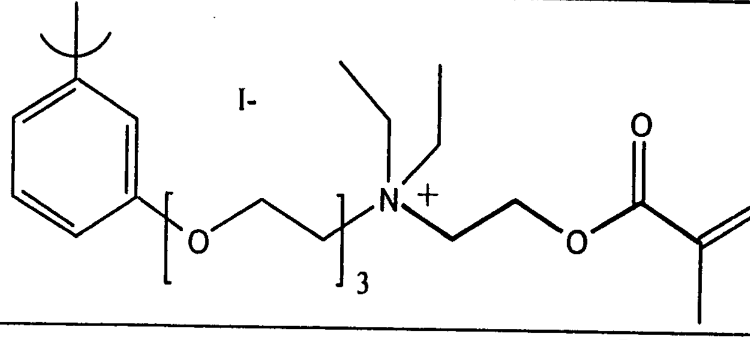
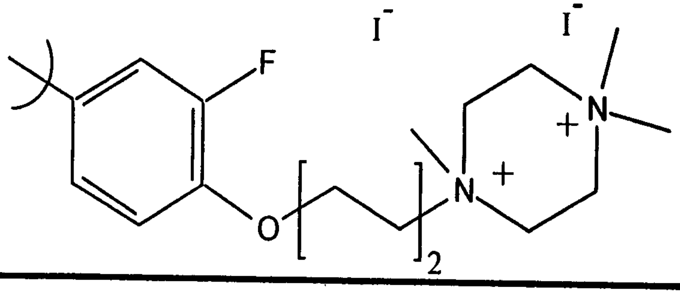
1374	n-butyl	n-butyl	OH	H	
1375	n-butyl	n-butyl	OH	H	
1376	n-butyl	n-butyl	OH	H	

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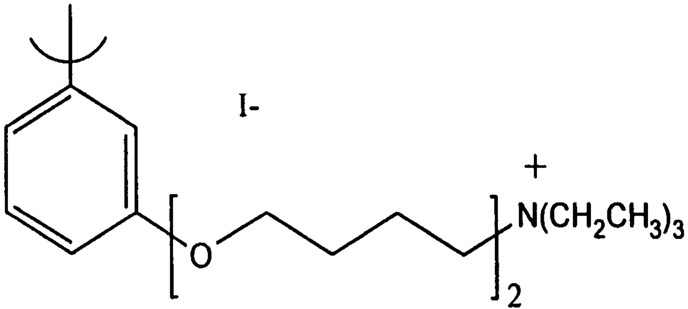
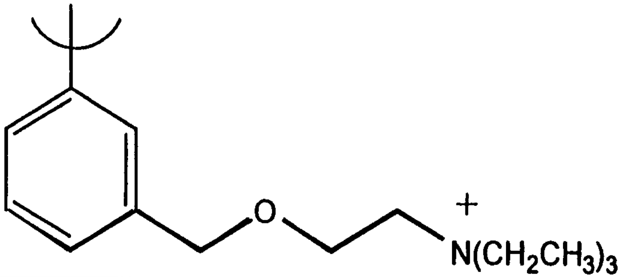
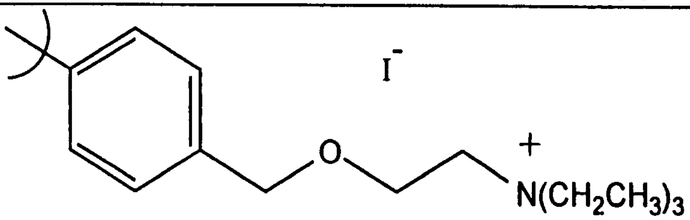
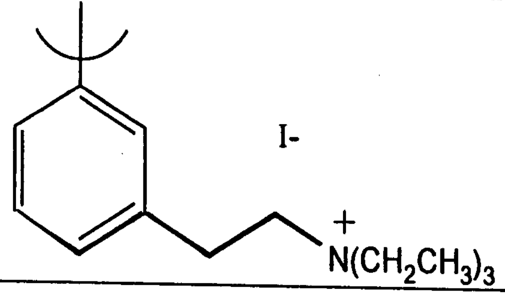
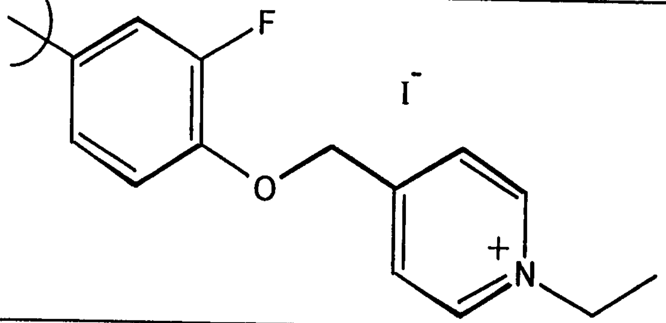
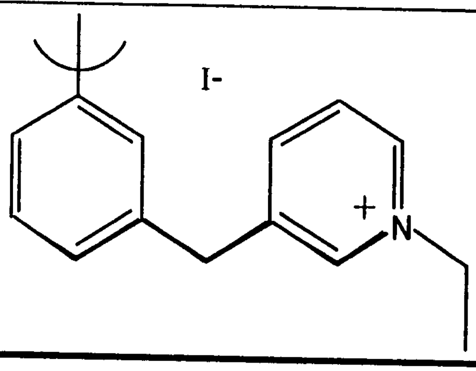
1377	n-butyl	n-butyl	OH	H	
1378	n-butyl	n-butyl	OH	H	
1379	n-butyl	n-butyl	OH	H	

1380	n-butyl	n-butyl	OH	H	
1381	n-butyl	n-butyl	OH	H	
1382	n-butyl	n-butyl	OH	H	

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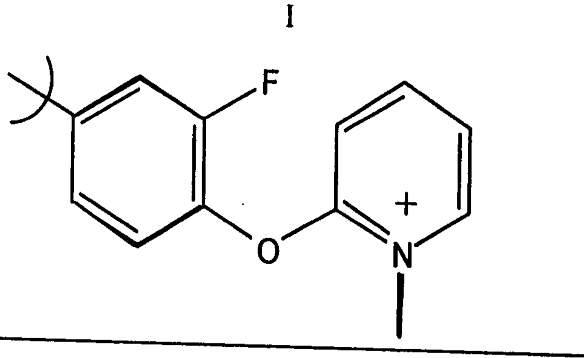
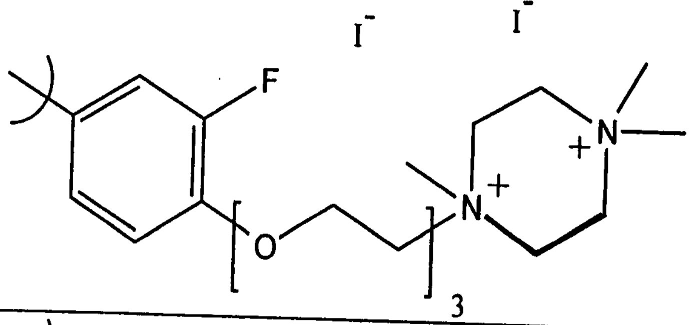
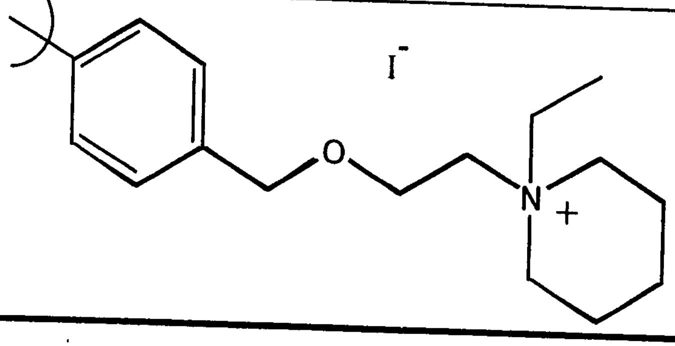
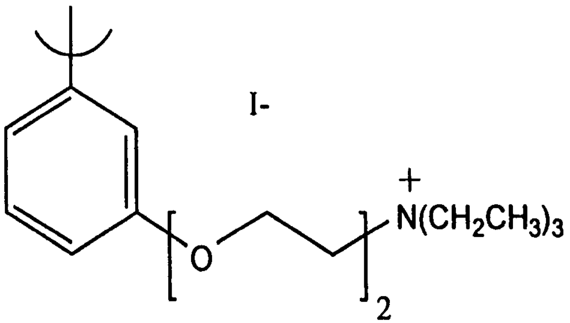
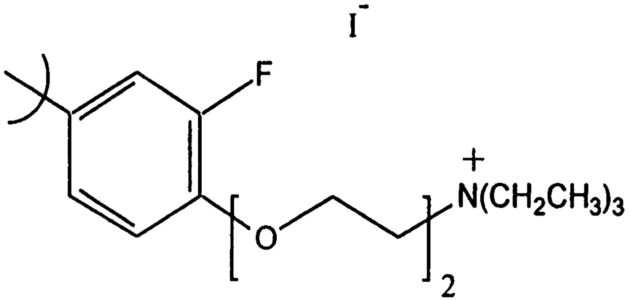
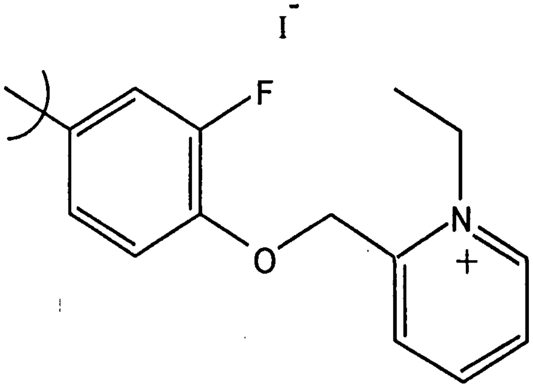
1383	n-butyl	n-butyl	OH	H	
1384	n-butyl	n-butyl	OH	H	
1385	n-butyl	n-butyl	OH	H	

1386	n-butyl	n-butyl	OH	H	
1387	n-butyl	n-butyl	OH	H	
1388	n-butyl	n-butyl	OH	H	

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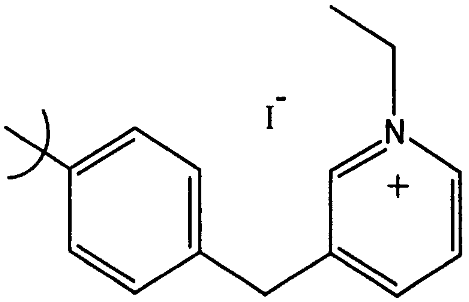
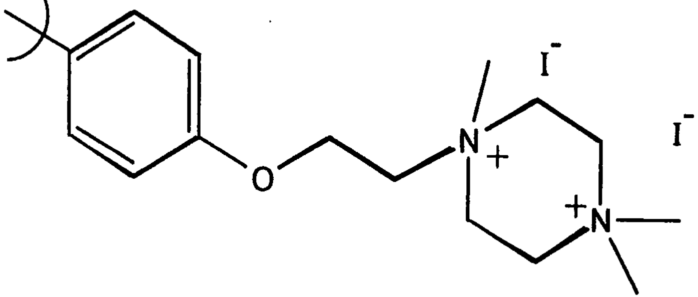
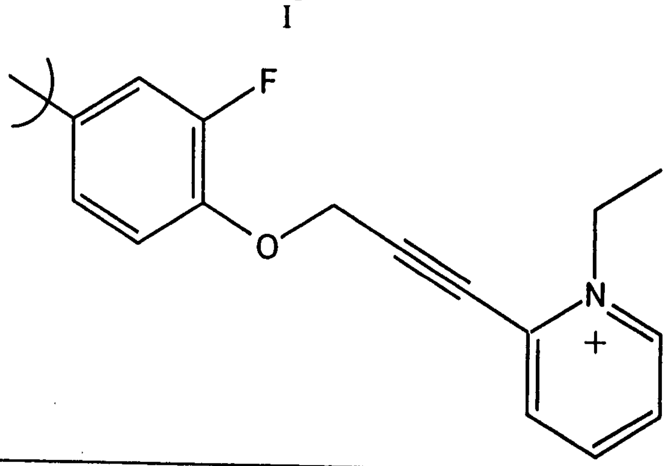
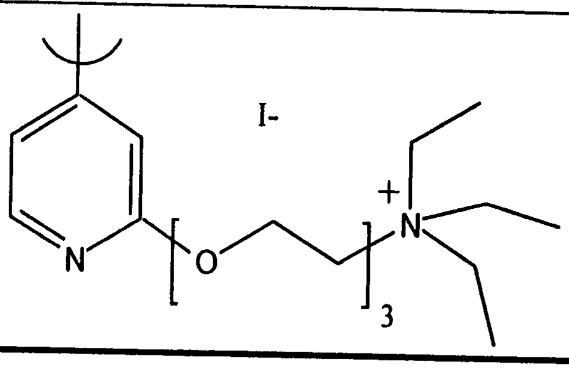
1389	n-butyl	n-butyl	OH	H	
1390	n-butyl	n-butyl	OH	H	

1391	n-butyl	n-butyl	OH	H	
1392	n-butyl	n-butyl	OH	H	

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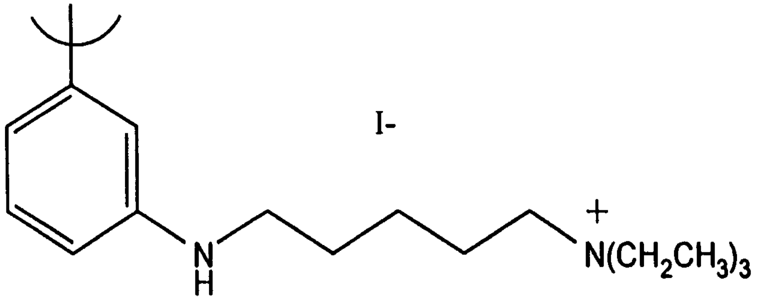
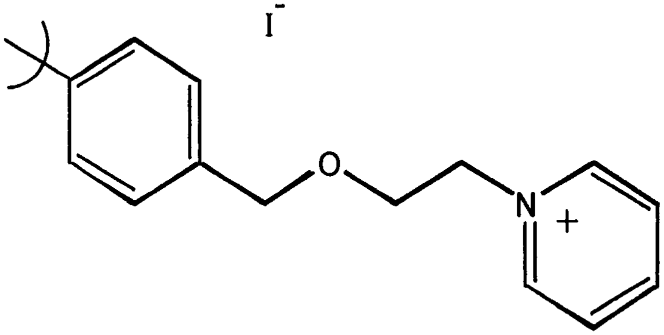
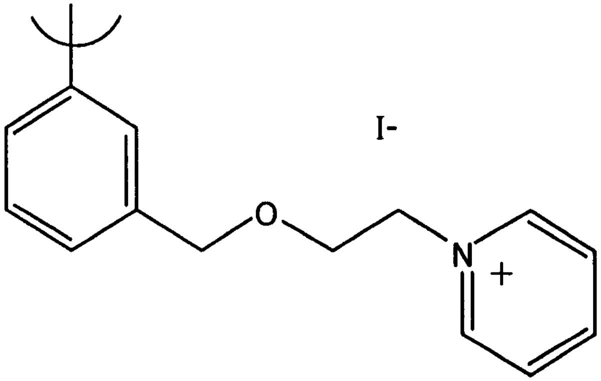
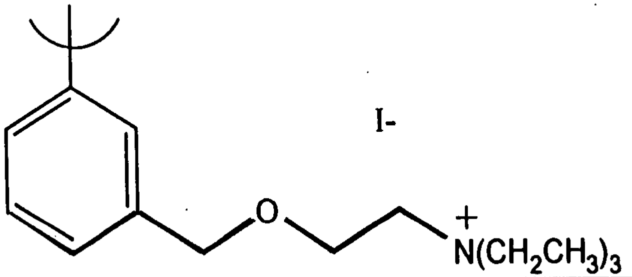
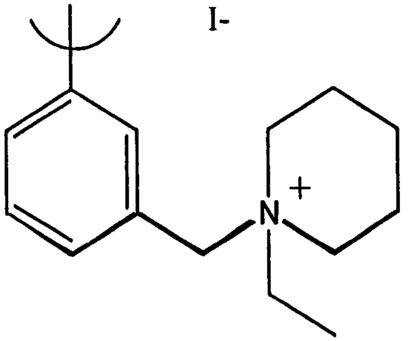
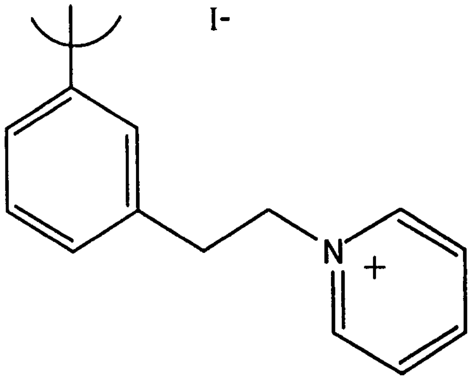
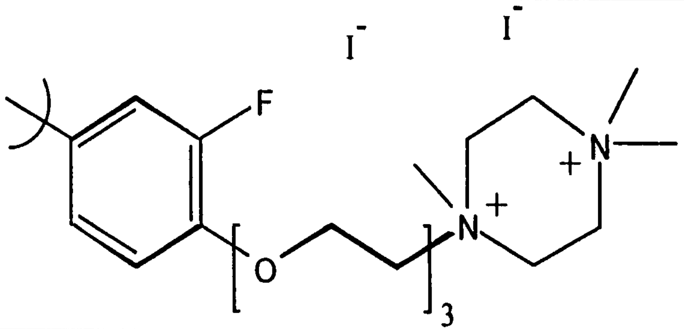
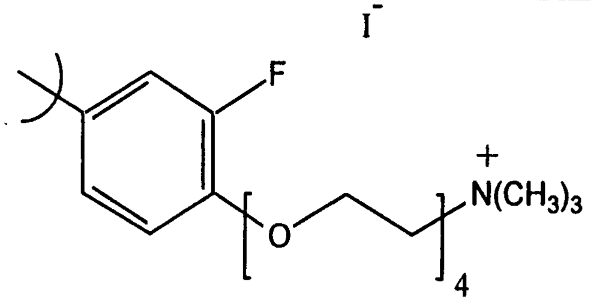
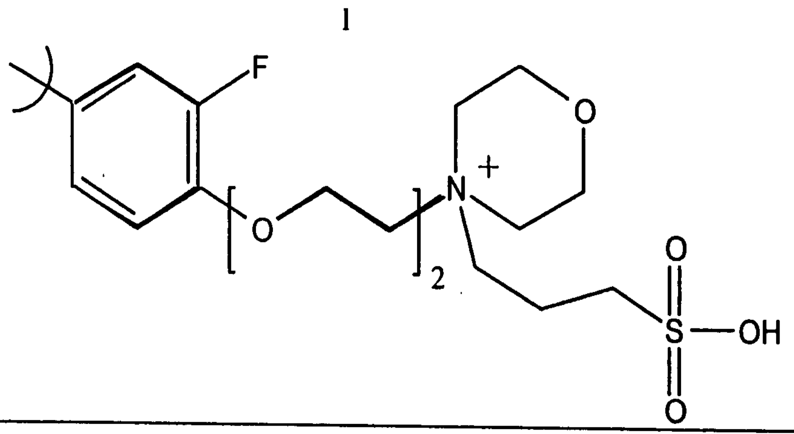
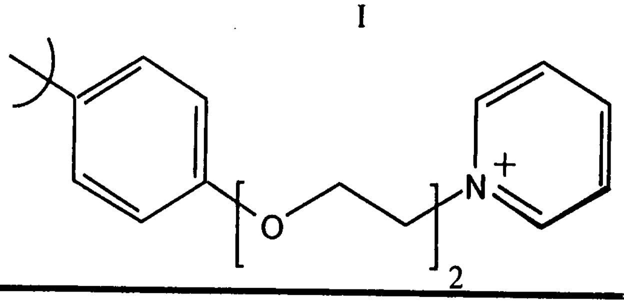
1393	n-butyl	n-butyl	OH	H	 I- N H + N(CH₂CH₃)₃
1394	n-butyl	n-butyl	OH	H	
1395	n-butyl	n-butyl	OH	H	

1396	n-butyl	n-butyl	OH	H	 I- O + N(CH2CH3)3
1397	n-butyl	n-butyl	OH	H	
1398	n-butyl	n-butyl	OH	H	

1399	n-butyl	n-butyl	OH	H	
1400	n-butyl	n-butyl	OH	H	

1401	n-butyl	n-butyl	OH	H	
1402	n-butyl	n-butyl	OH	H	

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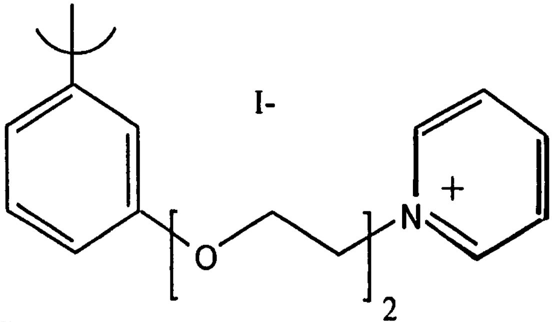
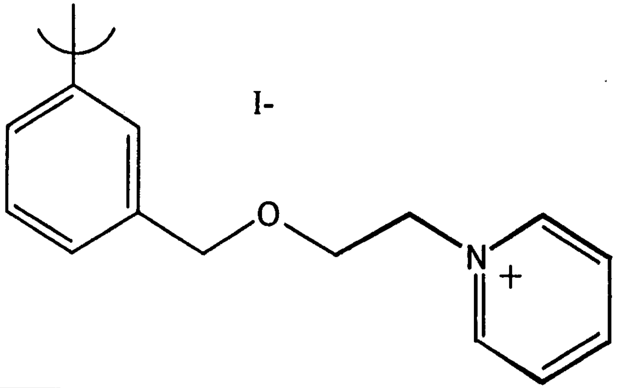
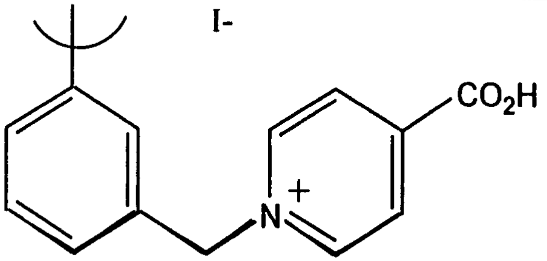
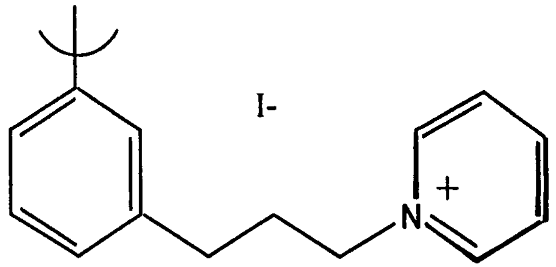
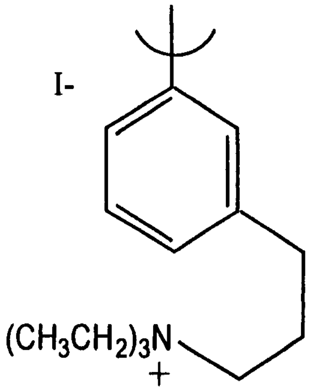
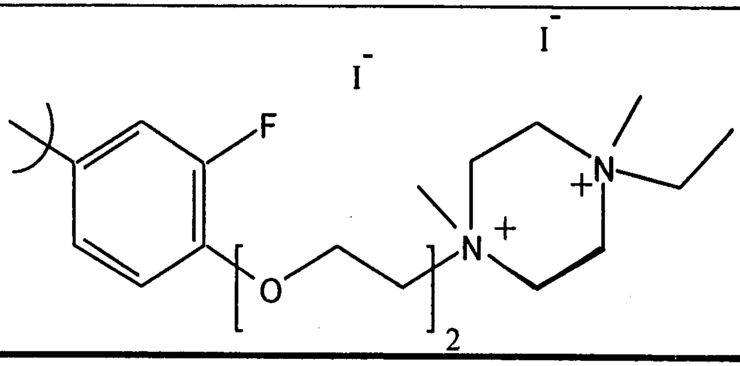
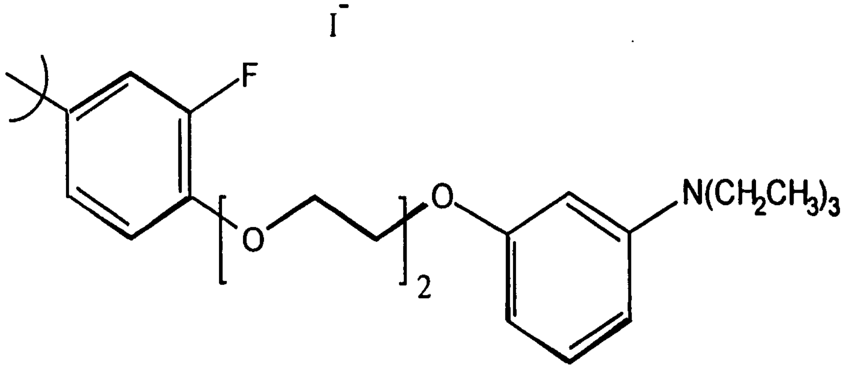
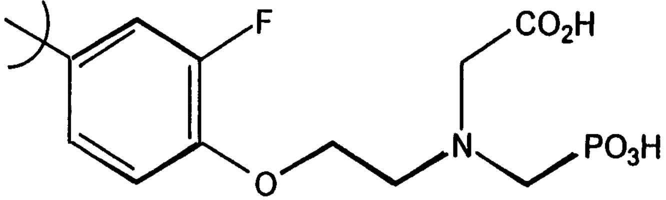
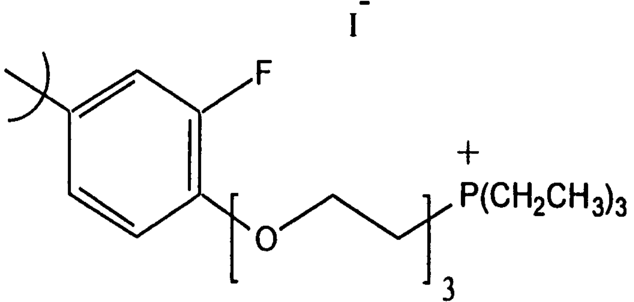
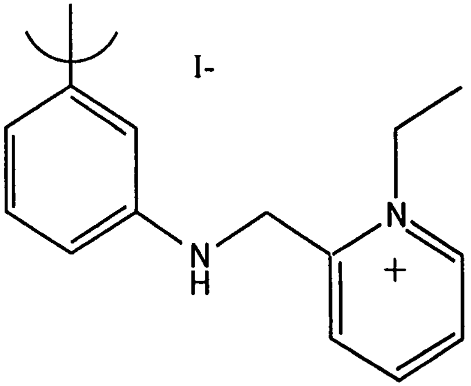
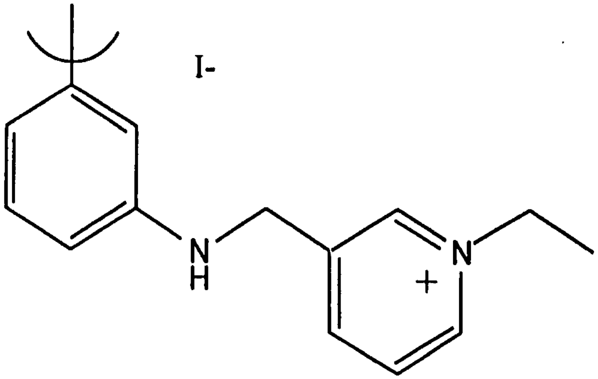
1403	n-butyl	n-butyl	OH	H	
1404	n-butyl	n-butyl	OH	H	
1405	n-butyl	n-butyl	OH	H	

1406	n-butyl	n-butyl	OH	H	
1407	n-butyl	n-butyl	OH	H	
1408	n-butyl	n-butyl	OH	H	

1409	n-butyl	n-butyl	OH	H	
1410	n-butyl	n-butyl	OH	H	
1411	n-butyl	n-butyl	OH	H	

1412	n-butyl	n-butyl	OH	H	
1413	n-butyl	n-butyl	OH	H	

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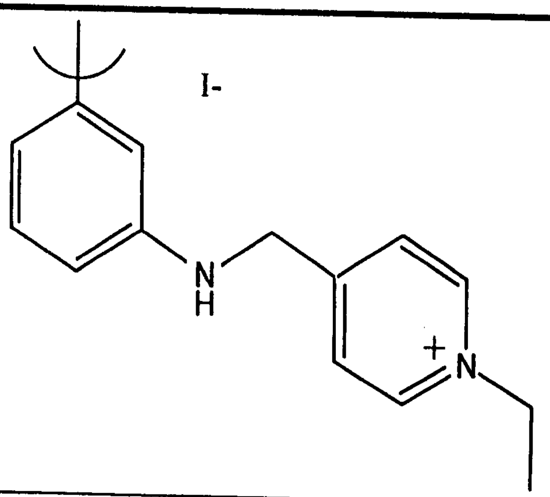
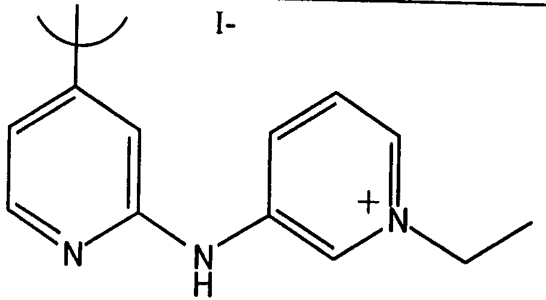
1414	n-butyl	n-butyl	OH	H	
1415	n-butyl	n-butyl	OH	H	

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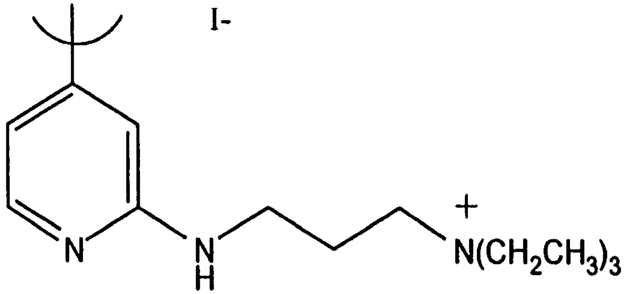
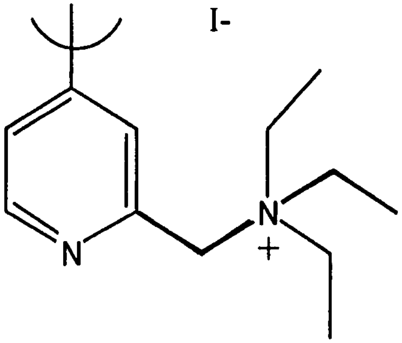
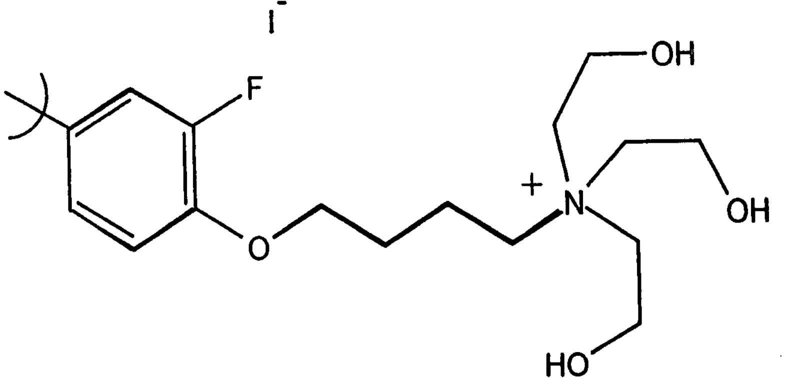
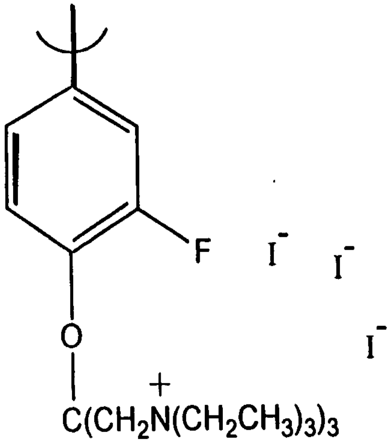
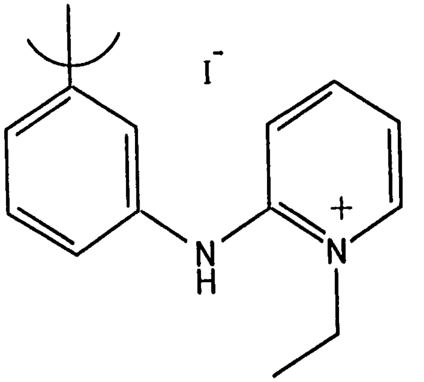
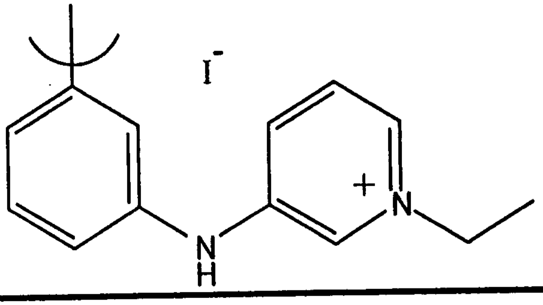
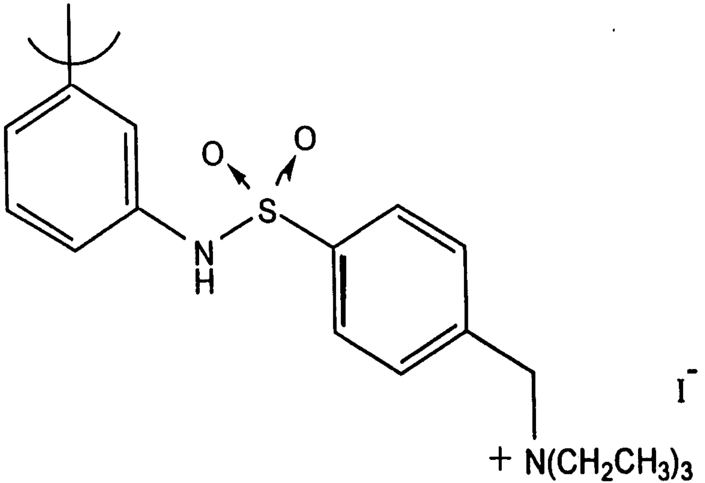
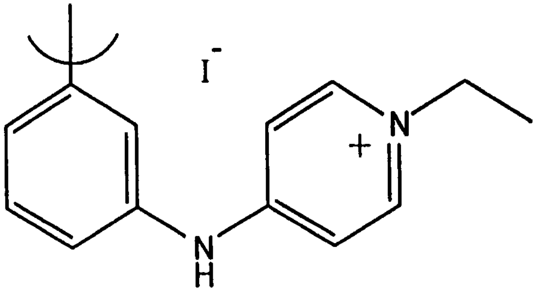
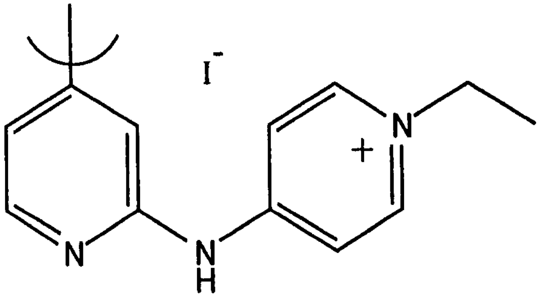
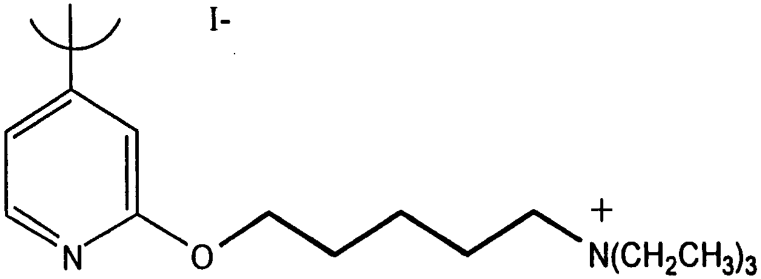
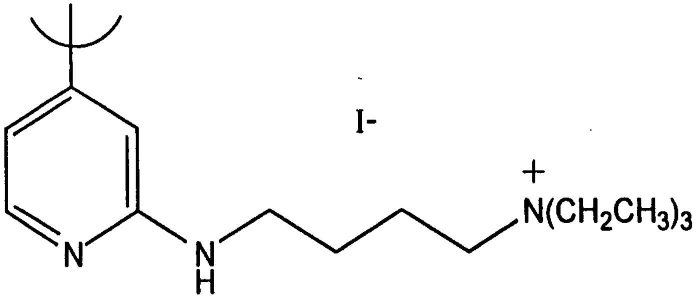
1416	n-butyl	n-butyl	OH	H	
1417	n-butyl	n-butyl	OH	H	

1418	n-butyl	n-butyl	OH	H	
1419	n-butyl	n-butyl	OH	H	

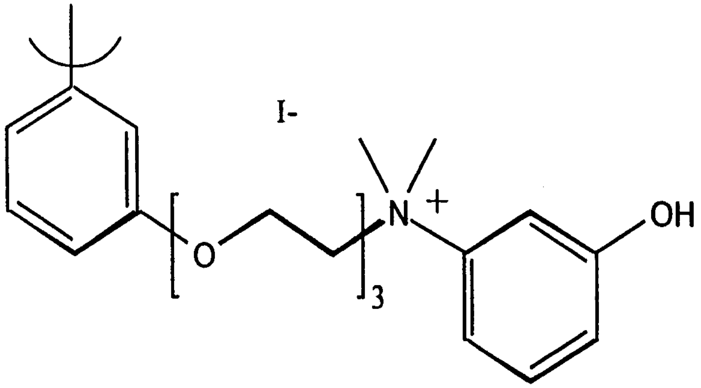
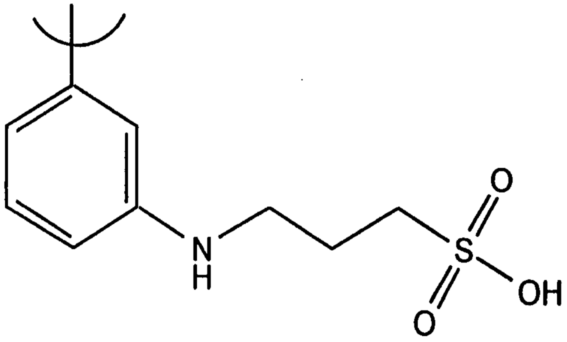
1420	n-butyl	n-butyl	OH	H	
1421	n-butyl	n-butyl	OH	H	

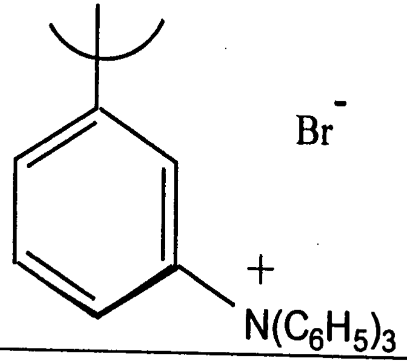
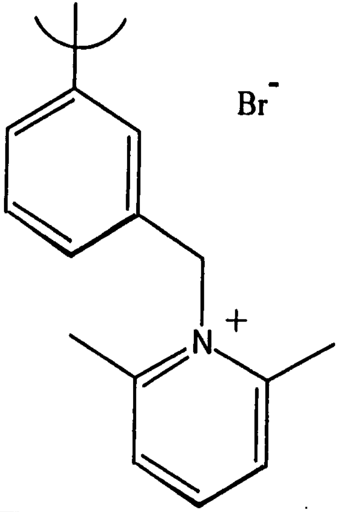
1422	n-butyl	n-butyl	OH	H	
1423	n-butyl	n-butyl	OH	H	

10068297 .020802

1424	n-butyl	n-butyl	OH	H	
1425	n-butyl	n-butyl	OH	H	 I- N O + N(CH2CH3)3
1426	n-butyl	n-butyl	OH	H	 I- N N H + N(CH2CH3)3

10068297.020802

1427	n-butyl	n-butyl	OH	H	
1428	n-butyl	n-butyl	OH	H	

1429	n-butyl	n-butyl	OH	H	
1430	n-butyl	n-butyl	OH	H	

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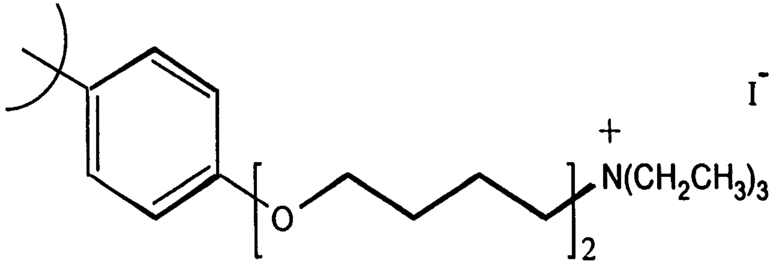
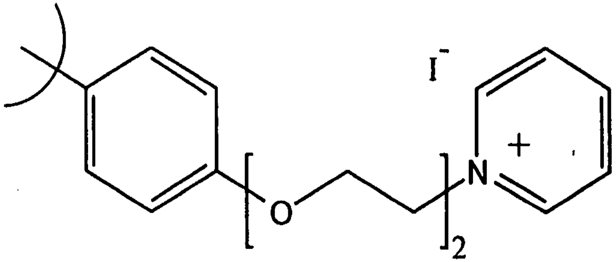
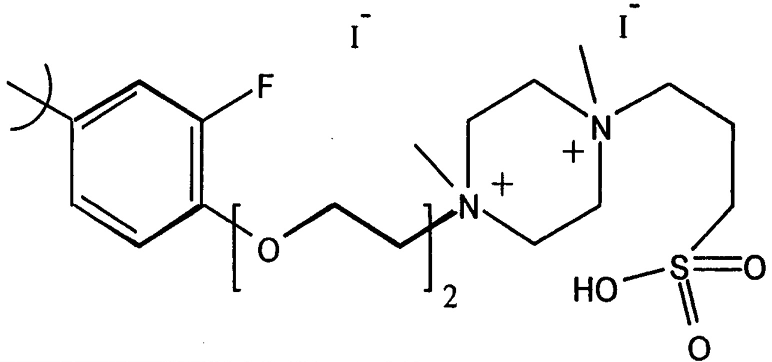
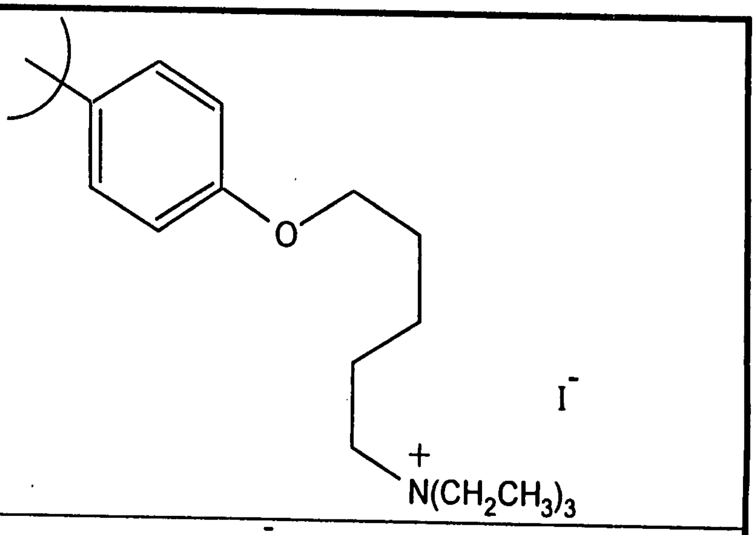
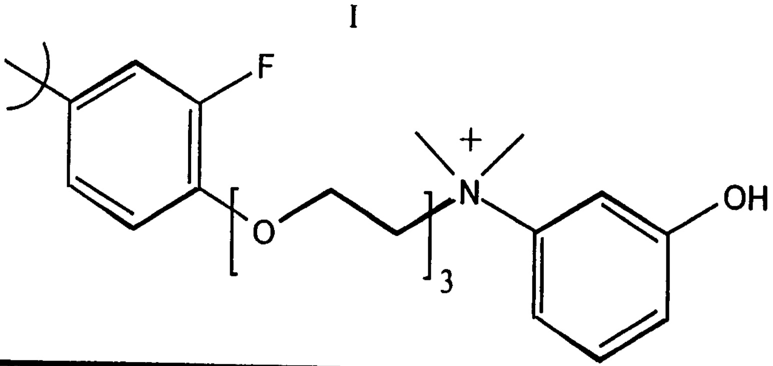
1431	n-butyl	n-butyl	OH	H	
1432	n-butyl	n-butyl	OH	H	
1433	n-butyl	n-butyl	OH	H	

1434	n-butyl	n-butyl	OH	H	
1435	n-butyl	n-butyl	OH	H	

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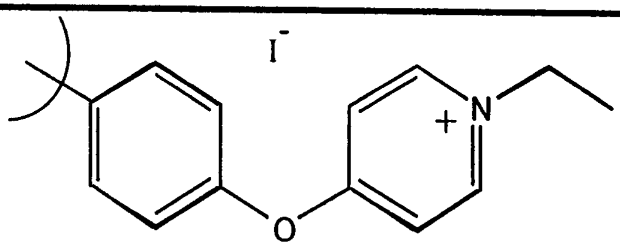
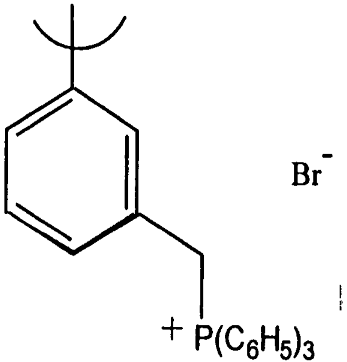
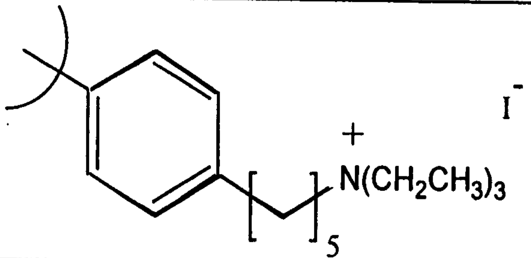
1436	n-butyl	n-butyl	OH	H	
1437	n-butyl	n-butyl	OH	H	
1438	n-butyl	n-butyl	OH	H	

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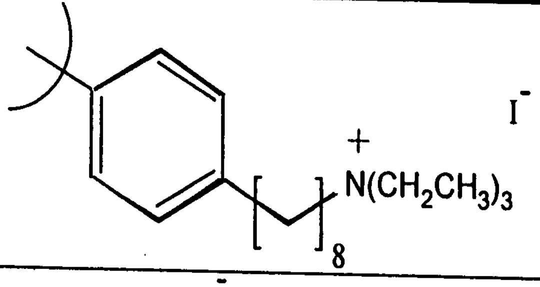
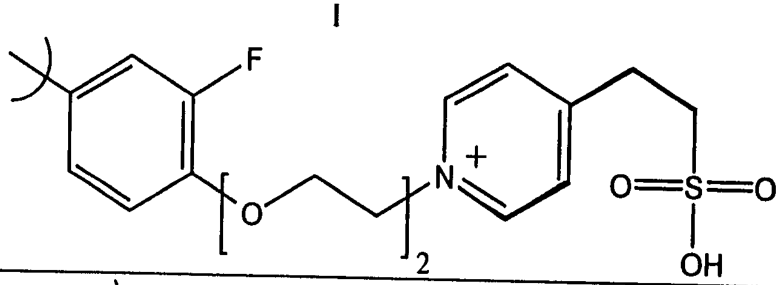
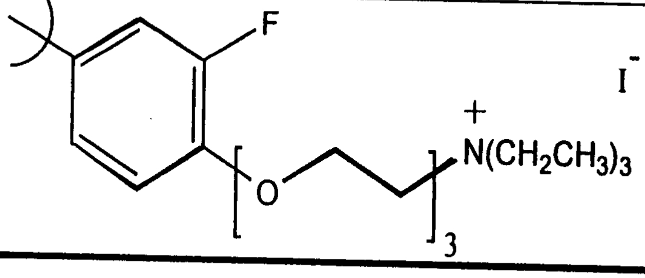
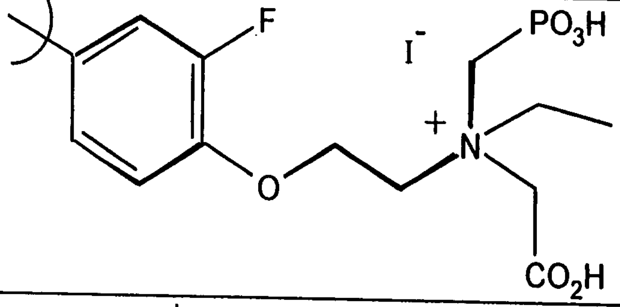
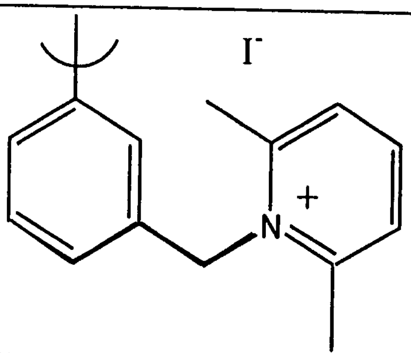
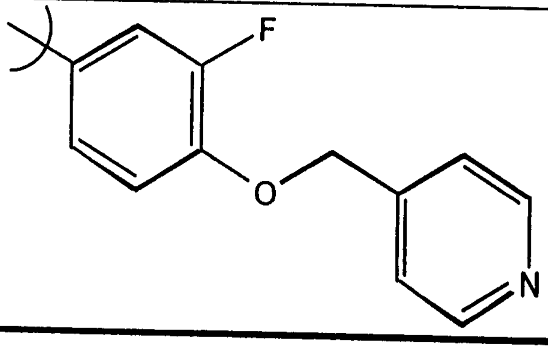
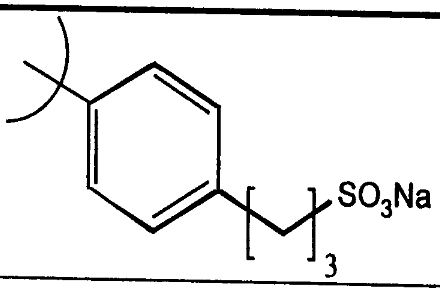
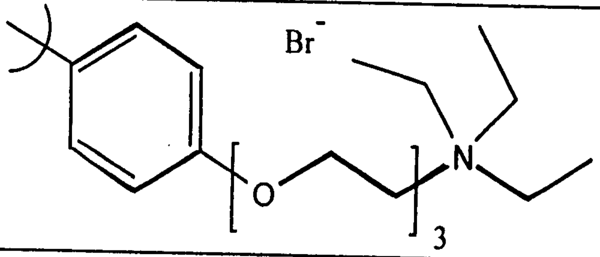
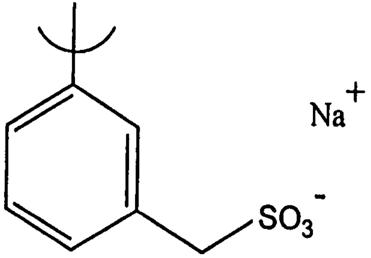
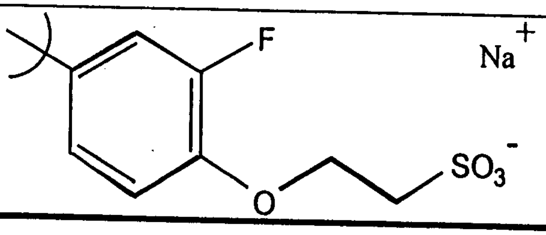
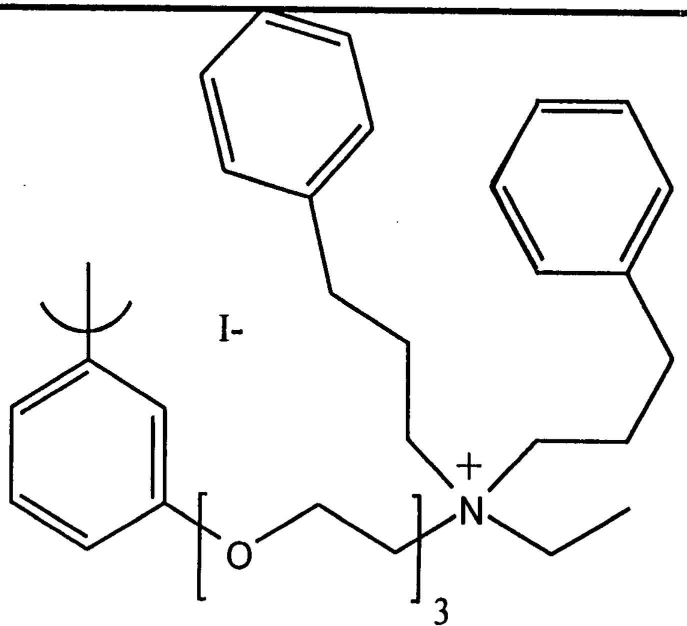
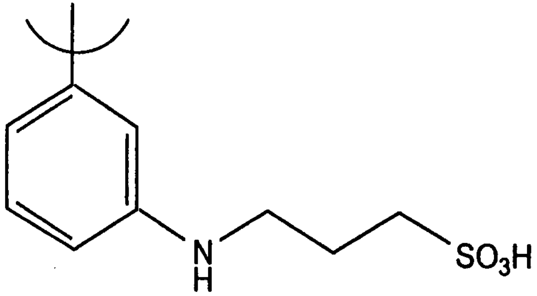
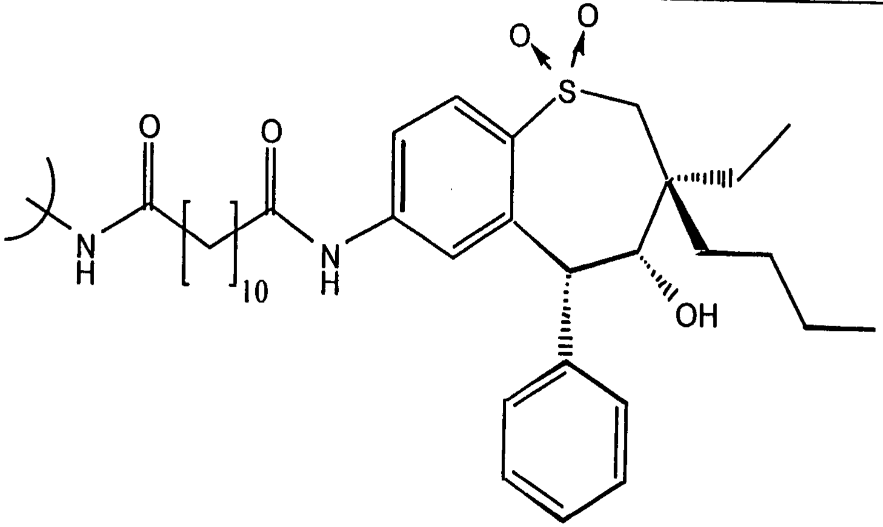
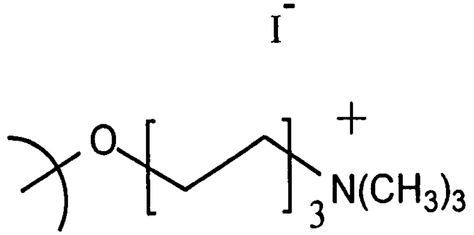
1439	n-butyl	n-butyl	OH	H	 I- + N(CH2CH3)3 8
1440	n-butyl	n-butyl	OH	H	 I- F O 2 N+ O=S=O OH
1441	n-butyl	n-butyl	OH	H	 F I- + N(CH2CH3)3 O 3

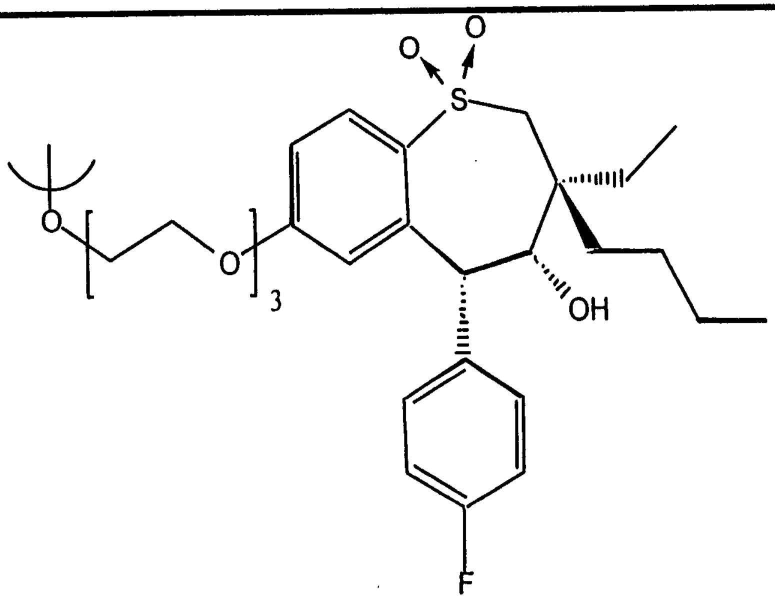
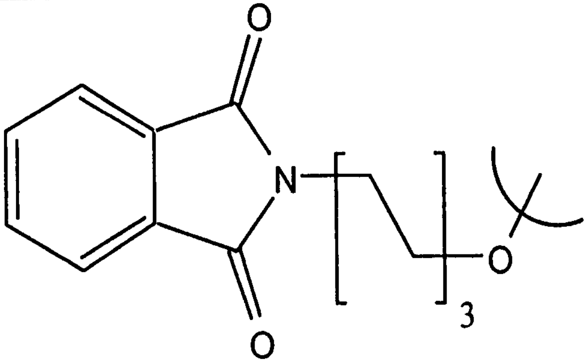
1442	n-butyl	n-butyl	OH	H	 F I⁻ + N O PO3H CO2H
1443	n-butyl	n-butyl	OH	H	
1444	n-butyl	n-butyl	OH	H	

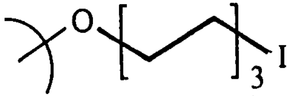
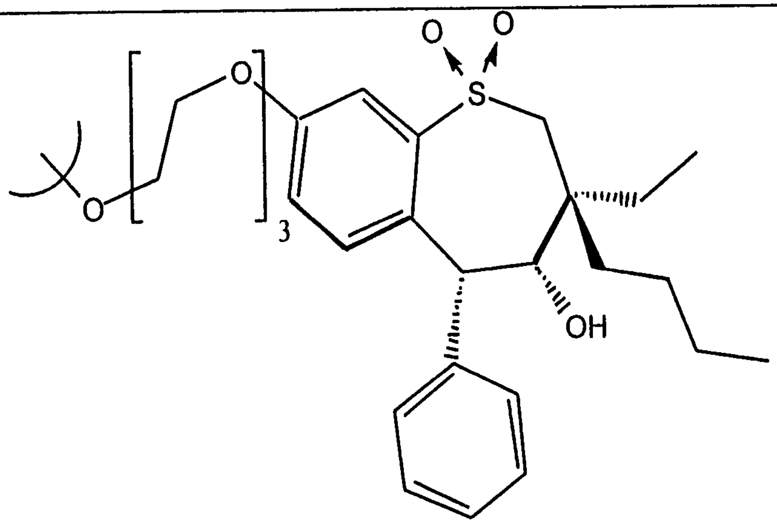
1445	n-butyl	n-butyl	OH	H	
1446	n-butyl	n-butyl	OH	H	
1447	n-butyl	n-butyl	OH	H	
1448	n-butyl	n-butyl	OH	H	

1449	n-butyl	n-butyl	OH	H	
1450	n-butyl	n-butyl	OH	H	phenyl
1451	n-butyl	n-butyl	OH	H	

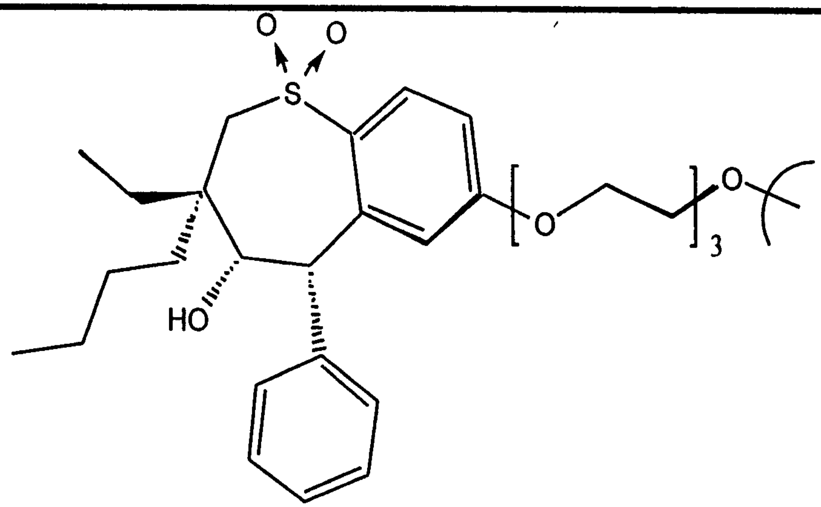
Compound Number	R^6	$(R^x)_q$
101	H	 at the 7-position
102	H	7-trimethylammonium iodide
103	H	7-trimethylammonium iodide
104	H	7-dimethylamino
105	H	7-methanesulfonamido
106	H	7-(2'-bromoacetamido)
107	H	7-amino
108	H	7-(hexylamido)
109	H	7-amino
110	H	7-acetamido
111	H	7-amino

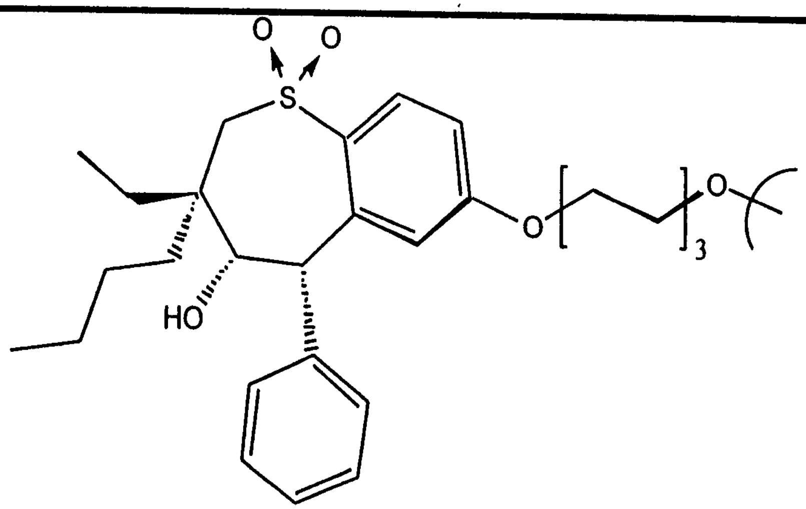
I12	H	7-amino
I13	H	7-amino
I14	H	7-amino
I15	H	7-(O-benzylcarbamato)
I16	H	7-(O-benzylcarbamato)
I17	H	7-(O-benzylcarbamato)
I18	H	7-(O-benzylcarbamato)
I19	H	7-(O-tert-butylcarbamato)
I20	H	7-(O-benzylcarbamato)
I21	H	7-amino
I22	H	7-amino
I23	H	7-hexylamino
I24	H	7-(hexylamino)
I25	H	 at the 8-position
I26	H	7-(O-benzylcarbamato)
I27	H	7-amino
I28	H	7-(O-benzylcarbamato)
I29	H	7-amino

131	H	 at the 7-position
132	H	 at the 8-position

133	H	8-(hexyloxy)
134	H	 at the 8-position
135	H	 at the 8-position
136	H	8-hydroxy

10068297.020802

137	H	 at the 7-position
138	H	8-acetoxy

139	H	 at the 7-position
140		
141		
142	3-methoxy-phenyl	7-methylmercapto
143	H	7-methylmercapto
144	H	7-(N-azetidinyl)
262	H	7-methoxy
263	3-methoxy-phenyl	7-methoxy
264	H	7-methoxy
265	3-trifluoro-methyl-phenyl	7-methoxy
266	H	7-hydroxy

267	H	7-methoxy
268	H	7-methoxy
269	4-fluoro-phenyl	7-methoxy
270	H	7-hydroxy
271	H	7-bromo
272	3-methoxy-phenyl	7-bromo
273	4-fluoro-phenyl	7-fluoro
274	H	7-fluoro
275	3-methoxy-phenyl	7-fluoro
276	H	7-fluoro
277	H	7-methoxy
278	H	7-methoxy
279	H	7-methoxy
280	H	7-methoxy
281	H	7-methylmercapto
282	H	7-methyl
283	4-fluoro-phenyl	7-methyl
284	H	7-(4'-morpholino)
286	H	7-(O-benzylcarbamato)
287	H	7-amino
288	H	7-amino
289	H	7-amino
290	H	7-amino
291	H	7-(O-benzylcarbamato)
292	H	7-amino

293	H	7-benzylamino
294	H	7-dimethylamino
295	H	7-amino
296	H	7-amino
1000	H	7-dimethylamino
1001	H	7-dimethylamino
1002	H	7-dimethylamino
1003	H	7-dimethylamino
1004	H	7-dimethylamino
1005	H	7-dimethylamino
1006	H	7-dimethylamino
1007	H	7-dimethylamino
1008	H	7-dimethylamino
1009	H	7-dimethylamino
1010	H	7-dimethylamino
1011	H	7-dimethylamino
1012	H	7-dimethylamino; 9-methoxy
1013	H	7-dimethylamino
1014	H	7-dimethylamino; 9-methoxy
1015	H	7-dimethylamino
1016	H	7-dimethylamino
1017	H	7-dimethylamino
1018	H	7-dimethylamino
1019	H	7-dimethylamino
1020	H	7-dimethylamino
1021	H	7-dimethylamino
1022	H	7-dimethylamino
1023	H	7-dimethylamino
1024	H	7-dimethylamino

1025	H	7-dimethylamino
1026	H	7-dimethylamino
1027	H	7-dimethylamino
1028	H	7-dimethylamino
1029	H	7-dimethylamino
1030	H	7-dimethylamino
1031	H	7-dimethylamino
1032	H	7-dimethylamino
1033	H	7-dimethylamino
1034	H	7-dimethylamino
1035	H	7-dimethylamino
1036	H	7-dimethylamino
1037	H	7-dimethylamino
1038	H	7-dimethylamino
1039	H	7-dimethylamino
1040	H	7-dimethylamino
1041	H	7-dimethylamino
1042	H	7-dimethylamino
1043	H	7-dimethylamino
1044	H	7-dimethylamino
1045	H	7-dimethylamino
1046	H	7-dimethylamino
1047	H	7-dimethylamino
1048	H	7-dimethylamino
1049	H	7-dimethylamino
1050	H	7-dimethylamino
1051	H	7-dimethylamino
1052	H	7-dimethylamino
1053	H	7-dimethylamino

1054	H	7-dimethylamino
1055	H	7-dimethylamino
1056	H	7-dimethylamino
1057	H	7-dimethylamino
1058	H	7-dimethylamino
1059	H	7-dimethylamino
1060	H	7-methylamino
1061	H	7-methylamino
1062	H	7-methylamino
1063	H	7-methylamino
1064	H	7-methylamino
1065	H	7-dimethylamino
1066	H	7-dimethylamino
1067	H	9-dimethylamino
1068	H	7-dimethylamino
1069	H	7-dimethylamino; 9-dimethylamino
1070	H	7-dimethylamino
1071	H	7-dimethylamino
1072	H	7-dimethylamino
1073	H	7-dimethylamino
1074	H	7-dimethylamino
1075	H	7-dimethylamino; 9-dimethylamino
1076	H	7-dimethylamino
1077	H	7-dimethylamino
1078	H	7-dimethylamino
1079	H	7-dimethylamino
1080	H	7-dimethylamino
1081	H	7-dimethylamino

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1082	H	7-dimethylamino
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1084	H	7-dimethylamino
1085	H	7-dimethylamino
1086	H	7-dimethylamino
1087	H	7-dimethylamino
1088	H	7-dimethylamino
1089	H	7-dimethylamino
1090	H	7-dimethylamino
1091	H	7-dimethylamino
1092	H	7-dimethylamino
1093	H	7-dimethylamino
1094	H	7-dimethylamino
1095	H	7-dimethylamino
1096	H	7-dimethylamino
1097	H	7-dimethylamino
1098	H	7-dimethylamino
1099	H	7-dimethylamino
1100	H	7-dimethylamino
1101	H	7-dimethylamino
1102	H	7-dimethylamino
1103	H	7-dimethylamino
1104	H	7-dimethylamino
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1106	H	7-dimethylamino
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1109	H	7-dimethylamino
1110	H	7-dimethylamino

1111	H	7-dimethylamino
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1122	H	7-dimethylamino
1123	H	7-dimethylamino
1124	H	7-dimethylamino
1125	H	7-dimethylamino
1126	H	7-dimethylamino
1127	H	7-dimethylamino
1128	H	7-dimethylamino
1129	H	9-dimethylamino
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1131	H	7-dimethylamino
1132	H	7-dimethylamino
1133	H	7-dimethylamino
1134	H	7-dimethylamino
1135	H	7-dimethylamino
1136	H	7-dimethylamino
1137	H	9-(2',2'-dimethylhydrazino)
1138	H	7-dimethylamino
1139	H	7-dimethylamino

1140	H	7-(2',2'-dimethylhydrazino)
1141	H	7-ethylmethylamino
1142	H	7-dimethylamino
1143	3-fluoro-4-methoxyphenyl	7-dimethylamino
1144	H	7-dimethylamino
1145	H	9-dimethylamino
1146	H	7-dimethylamino
1147	H	7-diethylamino
1148	H	7-dimethylsulfonium, fluoride salt
1149	H	7-ethylamino
1150	H	7-ethylmethylamino
1151	H	7-dimethylamino
1152	H	7-(ethoxymethyl) methylamino
1153	H	7-methylamino
1154	H	9-methoxy
1155	H	7-methyl
1156	H	7-methylmercapto
1157	H	7-fluoro; 9-dimethylamino
1158	H	7-methoxy
1159	H	7-dimethylamino
1160	H	7-diethylamino
1161	H	7-dimethylamino
1162	H	7-dimethylamino
1163	H	7-methoxy
1164	H	7-methoxy
1165	H	7-trimethylammonium iodide
1166	H	7-trimethylammonium iodide

I167	H	7-dimethylamino
I168	H	7-trimethylammonium iodide
I169	H	8-dimethylamino
I170	H	7-ethylpropylamino
I171	H	7-dimethylamino
I172	H	7-methoxy
I173	H	7-ethylpropylamino
I174	H	7-phenyl
I175	H	7-methylsulfonyl
I176	H	9-fluoro
I177	H	7-butylmethylamino
I178	H	7-dimethylamino
I179	H	8-methoxy
I180	H	7-trimethylammonium iodide
I181	H	7-butylmethylamino
I182	H	7-methoxy
I183	H	7-fluoro
I184	H	7-fluoro; 9-fluoro
I185	H	7-fluoro
I186	H	7-fluoro; 9-fluoro
I187	H	7-methyl
I188	H	7-trimethylammonium iodide
I189	H	7-trimethylammonium iodide
I190	H	7-bromo
I191	H	7-hydroxy
I192	H	7-hydroxy
I193	H	7-dimethylamino
I194	H	7-dimethylamino
I195	H	7-(4'-methylpiperazin-1-yl)

I196	H	7-methoxy
I197	H	7-(N-methylformamido)
I198	H	7-methoxy
I199	H	7-dimethylamino
I200	phenyl	7-dimethylamino
I201	H	7-methyl
I202	H	7-methoxy
I203	H	7-(4'-tert-butylphenyl)
I204	H	7-methoxy
I205	H	7-dimethylamino
I206	H	7-dimethylamino
I207	H	7-dimethylamino
I208	H	7-dimethylamino
I209	H	7-dimethylphenyl
I210	H	7-dimethylamino
I211	H	7-dimethylamino
I212	H	9-(4'-morpholino)
I213	3-fluoro-4-methoxy-phenyl	7-dimethylamino
I214	H	7-(N-methylformamido)
I215	H	9-methylmercapto
I216	H	7-bromo
I217	H	7-dimethylamino
I218	H	9-methylsulfonyl
I219	H	7-dimethylamino
I220	H	7-isopropylamino
I221	H	7-dimethylamino
I222	H	7-ethylamino
I223	H	8-bromo;

		7-methylamino
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1225	H	7-dimethylamino
1226	H	7-bromo
1227	H	7-(tert-butylamino
1228	H	8-bromo; 7-dimethylamino
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1230	H	9-dimethylamino; 7-fluoro
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1233	H	7-dimethylamino
1234	H	7-dimethylamino
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1241	H	7-dimethylamino
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1243	H	7-dimethylamino
1244	H	7-(1'-methylhydrazido)
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1247	H	7-dimethylamino
1248	H	7-dimethylamino
1249	H	7-dimethylamino
1250	H	7-dimethylamino

1251	H	7-dimethylamino
1252	H	7-dimethylamino
1253	H	7-dimethylamino
1254	H	7-dimethylamino
1255	H	7-dimethylamino
1256	H	7-dimethylamino
1257	H	8-bromo; 7-dimethylamino
1258	H	9-(tert-butylamino)
1259	phenyl	7-dimethylamino
1260	H	7-dimethylamino
1261	H	7-dimethylamino
1262	H	7-dimethylamino
1263	H	7-bromo
1264	H	7-isopropylamino
1265	H	9-isopropylamino
1266	H	7-dimethylamino
1267	H	7-carboxy, methyl ester
1268	H	7-dimethylamino
1269	H	7-dimethylamino
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1271	H	7-dimethylamino
1272	H	7-dimethylamino
1273	H	7-dimethylamino
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1276	H	7-dimethylamino
1277	H	7-dimethylamino
1278	H	7-dimethylamino
1279	H	7-dimethylamino

1280	H	7-dimethylamino
1281	H	7-dimethylamino
1282	H	7-trimethylammonium iodide
1283	H	7-dimethylamino
1284	H	9-ethylamino
1285	H	7-dimethylamino
1286	H	7-dimethylamino
1287	H	7-dimethylamino
1288	H	7-dimethylamino
1289	H	7-dimethylamino
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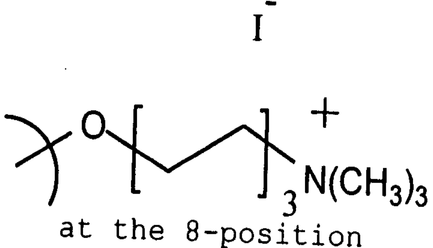
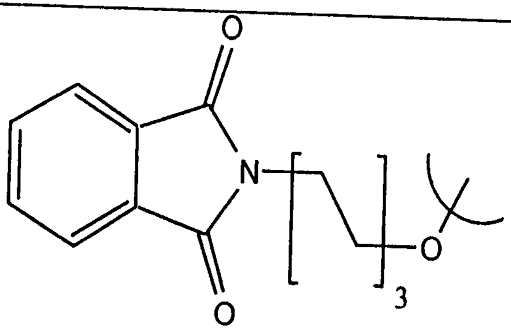
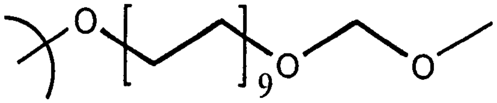
1296	H	7-dimethylamino
1297	H	7-dimethylamino
1298	H	7-dimethylamino
1299	H	7-dimethylamino
1300	phenyl	7-dimethylamino
1301	H	7-trimethylammonium iodide
1302	H	9-hydroxy
1303	H	7-dimethylamino
1304	H	7-tert-butylamino
1305	H	9-methylamino
1306	H	7-dimethylamino
1307	4-methoxyphenyl	9-(4'-morpholino)

1308	H	7-dimethylamino
1309	H	9-fluoro
1310	H	7-amino
1311	H	7-(hydroxylamino)
1312	H	8-hexyloxy
1313	H	8-ethoxy
1314	H	7-(hydroxylamino)
1315	H	7-(hexyloxy)
1316	H	8-hydroxy
1317	H	 at the 8-position
1318	H	7-dimethylamino
1319	H	7-fluoro
1320	H	7-amino
1321	H	 at the 8-position

1322	H	7-dimethylamino
1323	H	7-dimethylamino
1324	H	7-dimethylamino
1325	H	7-dimethylamino
1326	H	7-dimethylamino
1327	H	7-dimethylamino
1328	H	7-dimethylamino
1329	H	7-dimethylamino
1330	H	7-dimethylamino
1331	H	7-dimethylamino
1332	H	7-dimethylamino
1333	H	7-dimethylamino
1334	H	7-dimethylamino
1335	H	7-dimethylamino
1336	H	7-dimethylamino
1337	H	7-dimethylamino
1338	H	7-(4'-methylpiperazinyl)
1339	H	7-dimethylamino
1340	H	7-methyl
1341	H	7-dimethylamino
1342	H	7-(4'-fluorophenyl)
1343	H	7-amino
1344	H	7-dimethylamino
1345	H	7-trimethylammonium iodide
1346	H	 at the 8-position
1347	H	7-dimethylamino

1348	H	7-dimethylamino
1349	H	7-dimethylamino
1350	H	7-trimethylammonium iodide
1351	H	7-dimethylamino
1352	H	7-dimethylamino
1353	H	7-dimethylamino
1354	H	7-dimethylamino
1355	H	7-dimethylamino
1356	H	7-dimethylamino
1357	H	7-dimethylamino
1358	H	7-dimethylamino
1359	H	7-dimethylamino
1360	H	7-dimethylamino
1361	H	7-dimethylamino
1362	H	7-dimethylamino
1363	H	7-dimethylamino
1364	H	7-dimethylamino
1365	H	7-dimethylamino
1366	H	7-dimethylamino
1367	H	7-dimethylamino
1368	H	7-dimethylamino
1369	H	7-dimethylamino
1370	H	7-dimethylamino
1371	H	7-dimethylamino
1372	H	7-dimethylamino
1373	H	7-dimethylamino
1374	H	7-dimethylamino
1375	H	7-dimethylamino
1376	H	7-dimethylamino

1377	H	7-dimethylamino
1378	H	7-dimethylamino
1379	H	7-dimethylamino
1380	H	7-dimethylamino
1381	H	7-dimethylamino
1382	H	7-dimethylamino
1383	H	7-dimethylamino
1384	H	7-dimethylamino
1385	H	7-dimethylamino
1386	H	7-dimethylamino
1387	H	7-dimethylamino
1388	H	7-dimethylamino
1389	H	7-dimethylamino
1390	H	7-dimethylamino
1391	H	7-dimethylamino
1392	H	7-dimethylamino
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1394	H	7-dimethylamino
1395	H	7-dimethylamino
1396	H	7-dimethylamino
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1398	H	7-dimethylamino
1399	H	7-dimethylamino
1400	H	7-dimethylamino
1401	H	7-dimethylamino
1402	H	7-dimethylamino
1403	H	7-dimethylamino
1404	H	7-dimethylamino
1405	H	7-dimethylamino

1406	H	7-dimethylamino
1407	H	7-dimethylamino
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1419	H	7-dimethylamino
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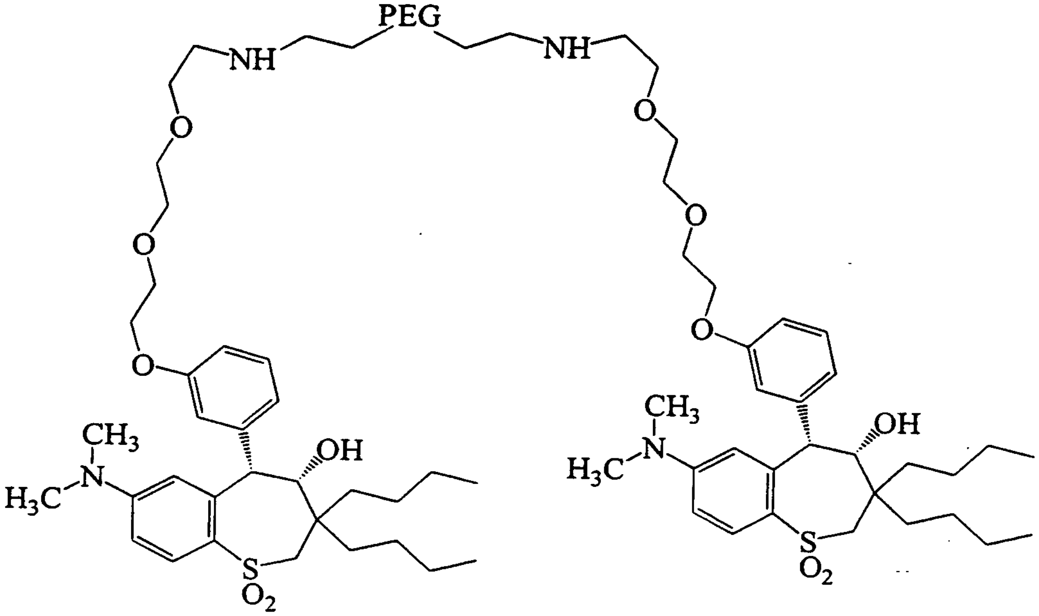
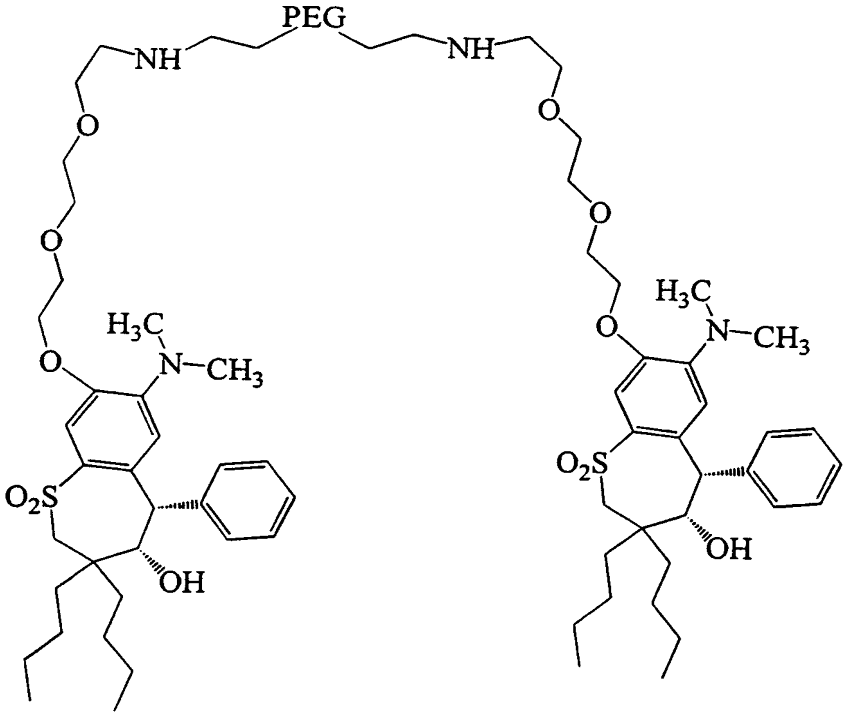
1421	H	7-dimethylamino
1422	H	7-dimethylamino
1423	H	7-dimethylamino
1424	H	7-dimethylamino
1425	H	7-dimethylamino
1426	H	7-dimethylamino
1427	H	7-dimethylamino
1428	H	7-dimethylamino
1429	H	7-dimethylamino
1430	H	7-dimethylamino
1431	H	7-dimethylamino
1432	H	7-dimethylamino
1433	H	7-dimethylamino
1434	H	7-dimethylamino

1435	H	7-dimethylamino
1436	H	7-dimethylamino
1437	H	7-dimethylamino
1438	H	7-dimethylamino
1439	H	7-dimethylamino
1440	H	7-dimethylamino
1441	H	7-dimethylamino
1442	H	7-dimethylamino
1443	H	7-dimethylamino
1444	H	7-dimethylamino
1445	H	7-dimethylamino
1446	H	7-methoxy; 8-methoxy
1447	H	7-dimethylamino
1448	H	7-dimethylamino
1449	H	7-dimethylamino

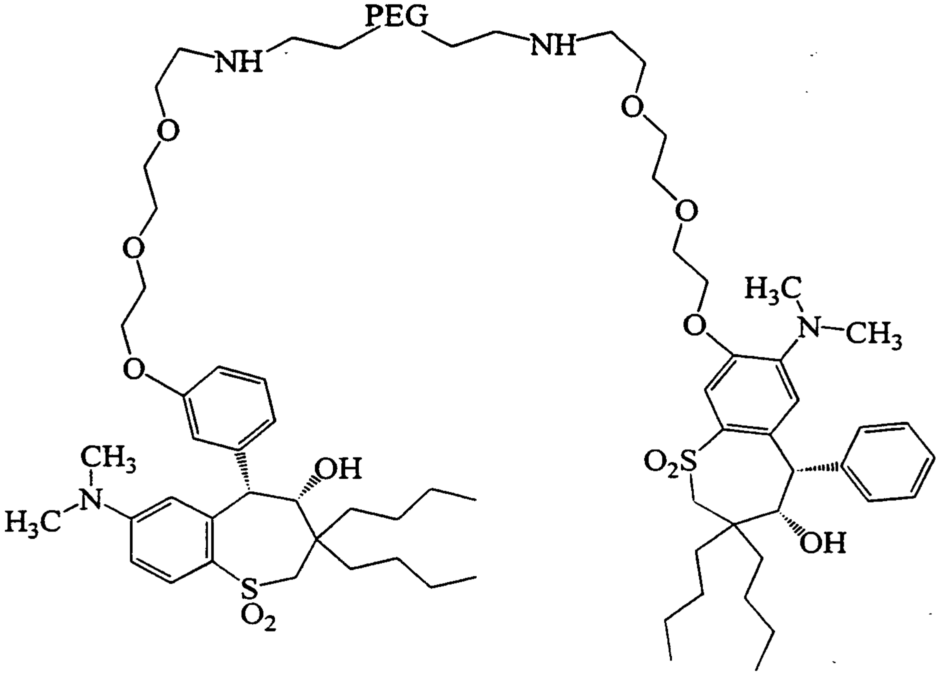
1450	H	7-dimethylamino
1451	H	7-dimethylamino


PEG
NH
NH
O
O
O
O
O
O
CH3
N
H3C
OH
S
O2
CH3
N
H3C
OH
S
O2

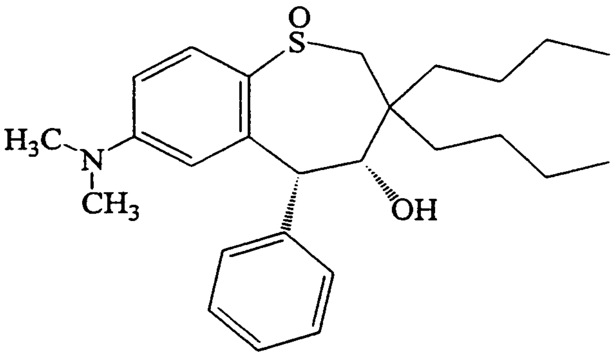
PEG = 3400 molecular weight polyethylene glycol polymer chain

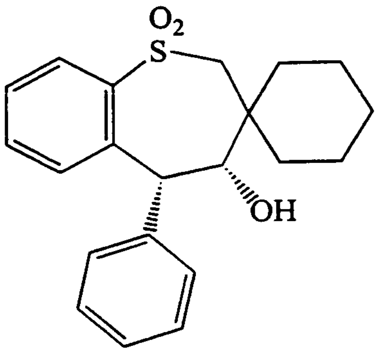

PEG
NH
NH
O
O
O
O
O
O
H3C
N
CH3
H3C
N
CH3
O2S
O2S
OH
OH

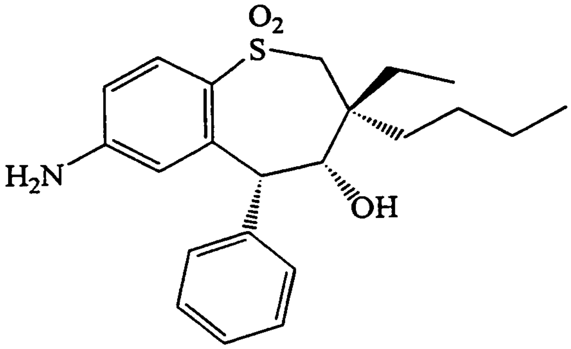
PEG = 3400 molecular weight polyethylene glycol polymer chain


PEG
NH
NH
O
O
O
O
O
O
H3C
N
CH3
CH3
N
H3C
OH
O2S
S
O2
OH

PEG = 3400 molecular weight polyethylene glycol polymer chain


O
S
H3C
N
CH3
OH


O2
S
OH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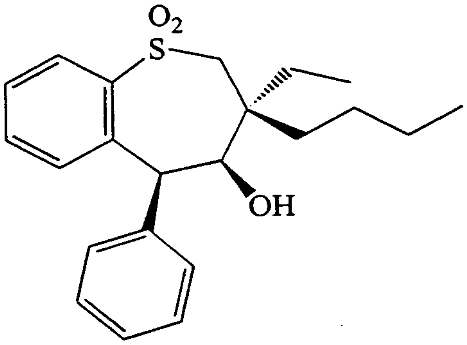
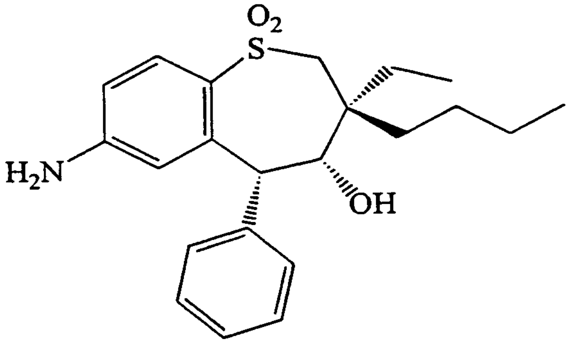
S
H2N
OH


O2
S
OH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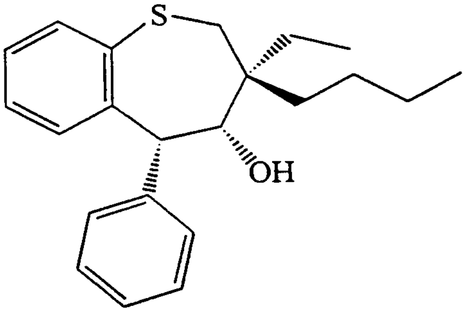
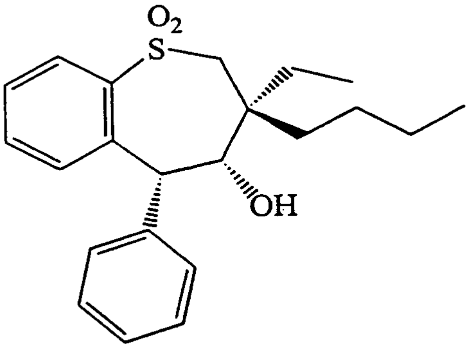
S
H2N
OH


S
OH


O2
S
OH

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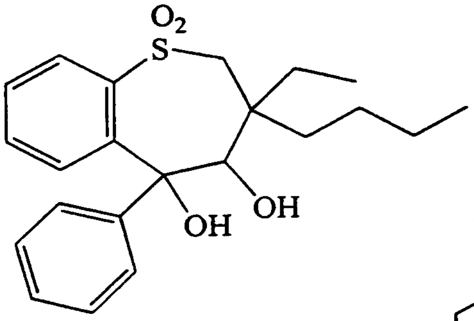

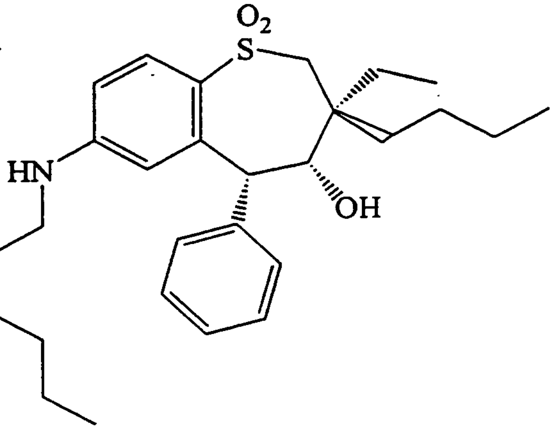

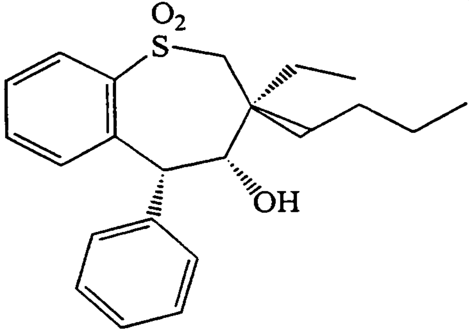

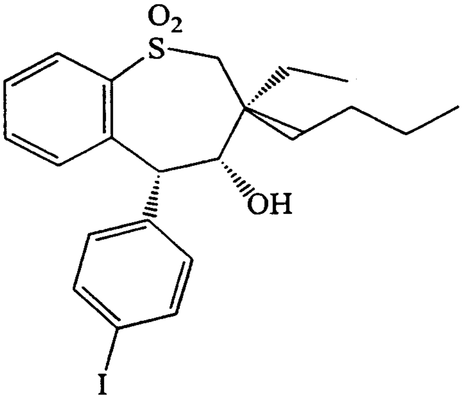

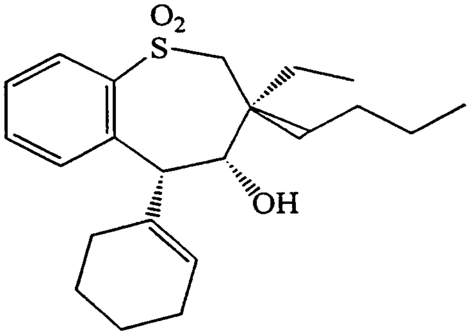

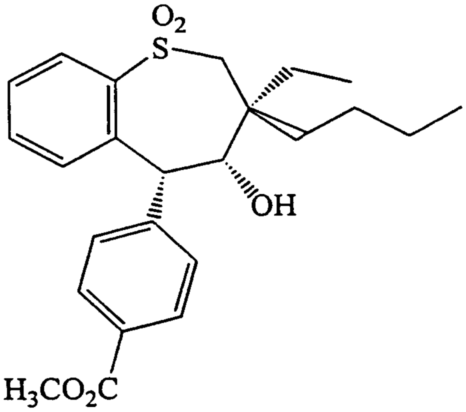

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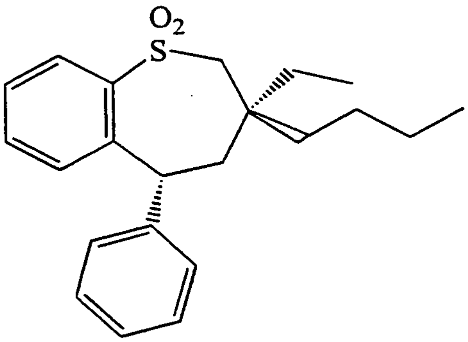
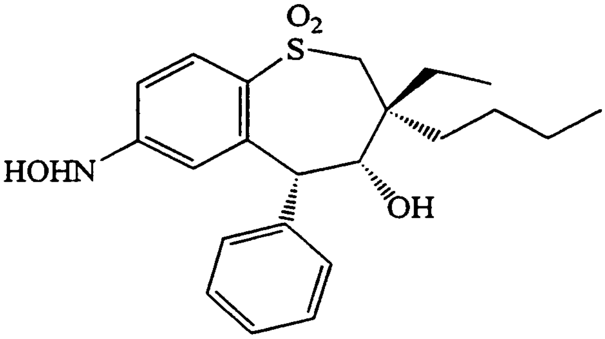
OH
H3CO2C

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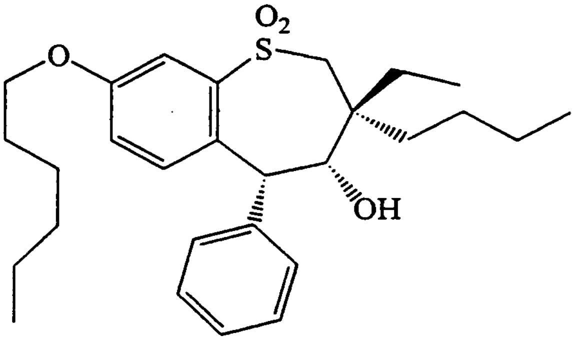
HOHN
OH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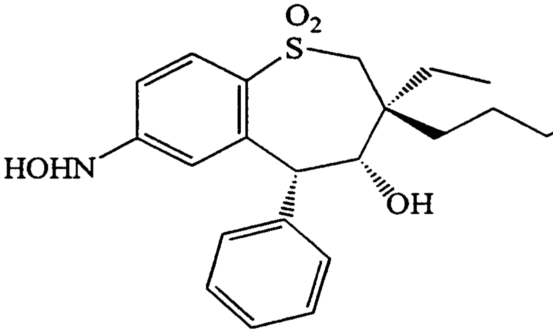
O
S
OH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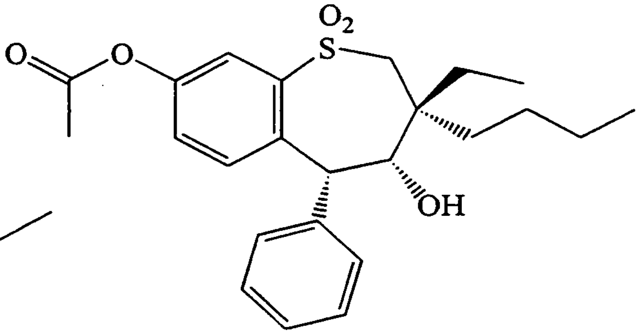
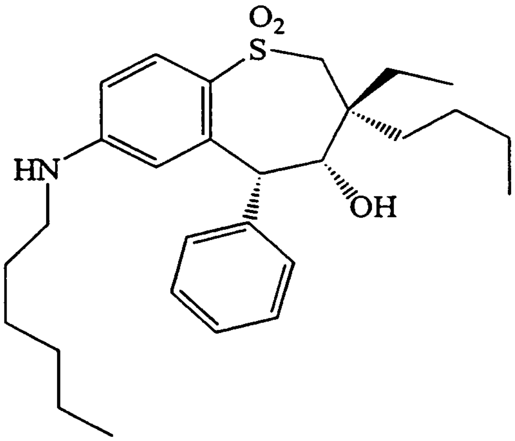
S
HOHN
OH


O2
O
O
S
OH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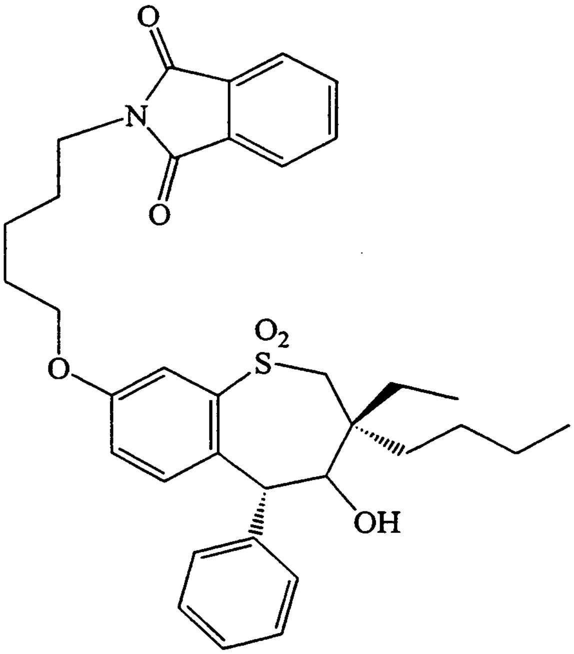
HN
OH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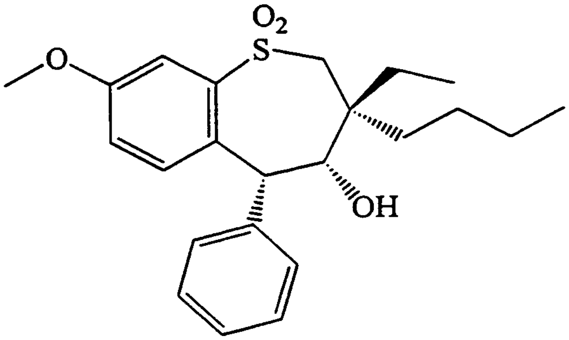
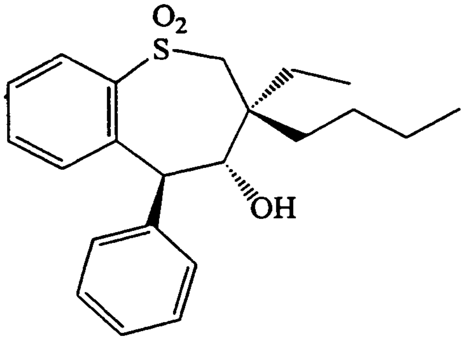
N
O
O
O2
S
OH


O
O2
S
OH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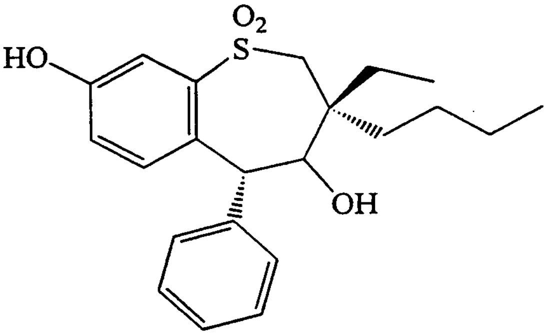
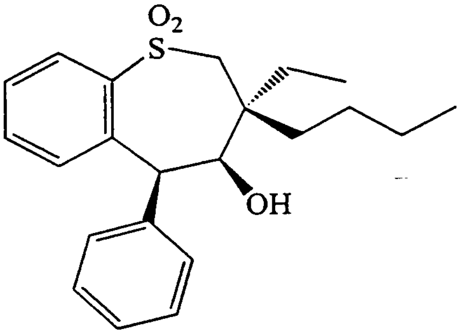
S
OH


HO
O2
S
OH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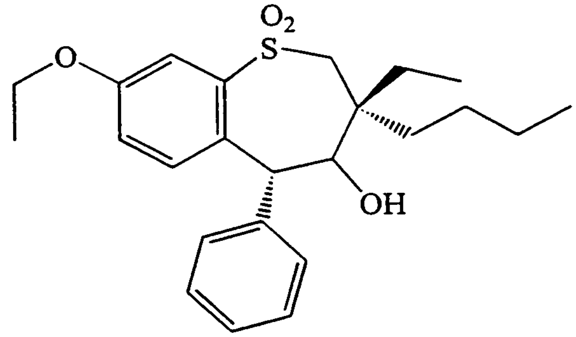
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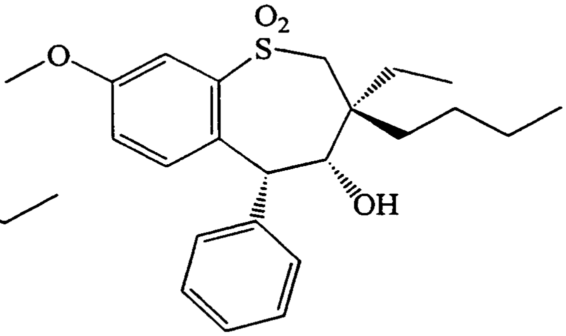
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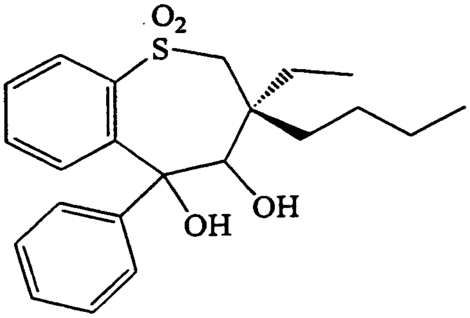
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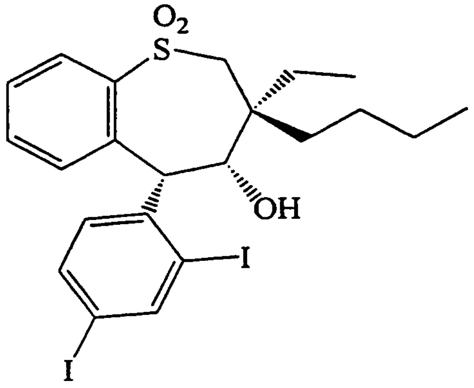
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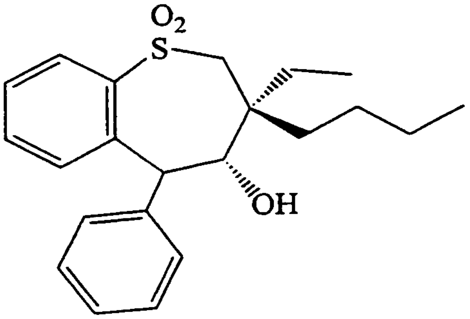
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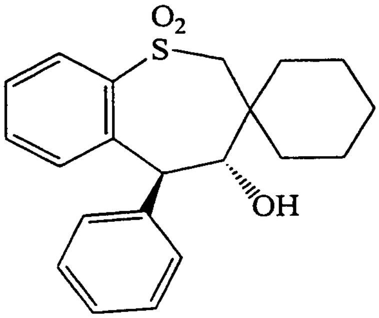
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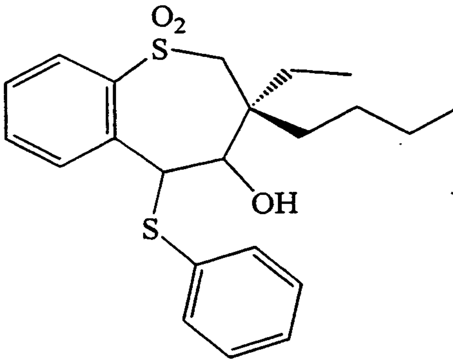
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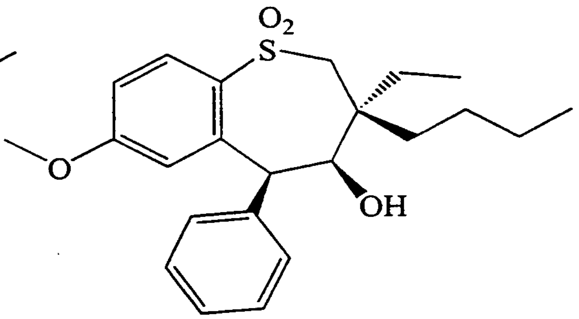
OH
S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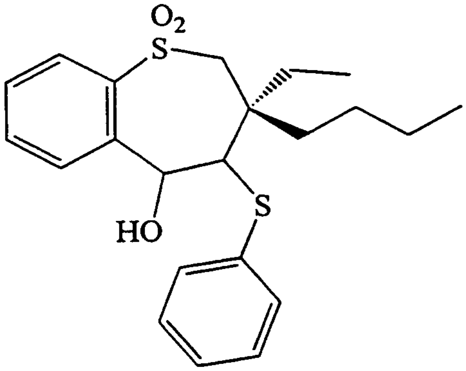
O
OH


O2
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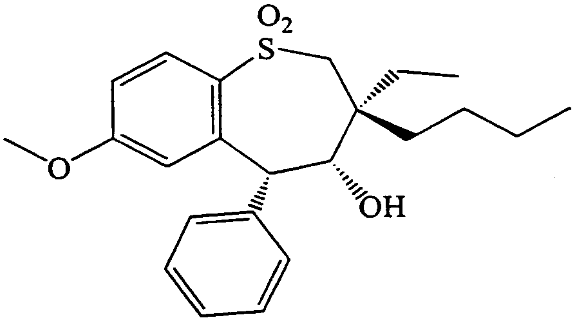
S
HO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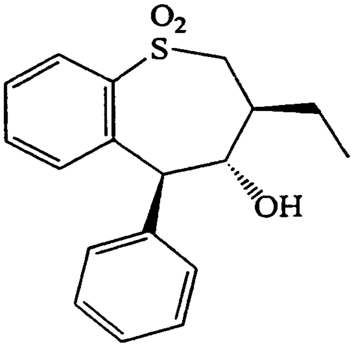
S
O
OH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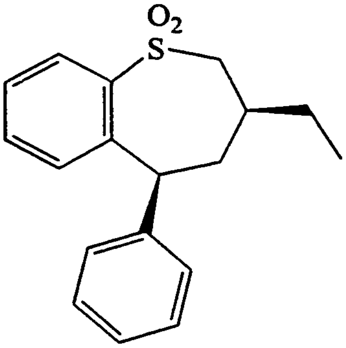
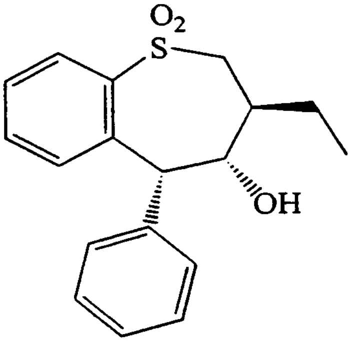
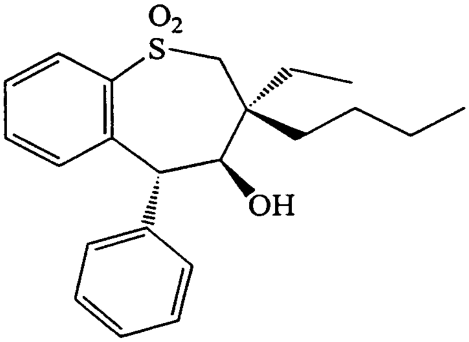
OH


O2
S


O2
S
OH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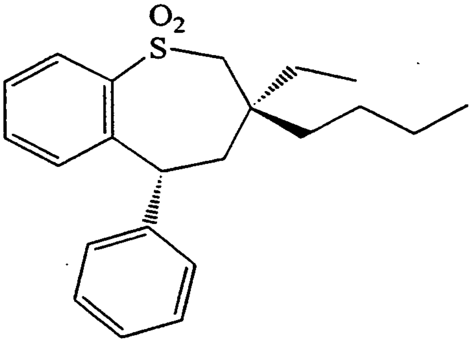

O2
S

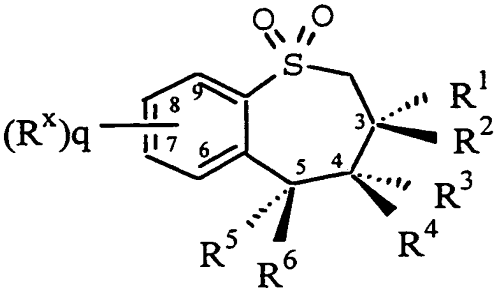
In further compounds of the present invention, R^5 and R^6 are independently selected from among hydrogen and ring-carbon substituted or unsubstituted aryl, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, pyrimidine, morpholine, N-alkylpyridinium, N-alkylpiperazinium, N-alkylmorpholinium, or furan in which the substituent(s) are selected from among halo, hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, N,N-dialkylamino, quaternary ammonium salts, a C_1 to C_4 alkylene bridge having a quaternary ammonium salt substituted thereon, alkoxycarbonyl, aryloxycarbonyl, alkylcarbonyloxy and arylcarbonyloxy, (O,O)-dioxyalkylene,

$-[O(CH_2)_w]_xX$ where x is 2 to 12, w is 2 or 3 and X comprises halo or a quaternary ammonium salt, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, or furan. The aryl group of R^5 or R^6 is preferably phenyl, phenylene, or benzene triyl, i.e., may be unsubstituted, mono-substituted, or di-substituted. Among the species which may constitute the substituents on the aryl ring of R^5 or R^6 are fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, trimethylammonium (preferably with an iodide or chloride counterion), methoxycarbonyl, ethoxycarbonyl, formyl, acetyl, propanoyl, (N)-hexyldimethylammonium, hexylenetrimethylammonium, tri(oxyethylene)iodide, and tetra(oxyethylene)trimethyl-ammonium iodide, each substituted at the p-position, the m-position, or both of the aryl ring. Other substituents that can be present on a phenylene, benzene triyl or other aromatic ring include 3,4-dioxymethylene (5-membered ring) and 3,4-dioxyethylene (6-membered ring). Among compounds which have been or can be demonstrated to have desirable ileal bile acid transport inhibiting properties are those in which R^5 or R^6 is selected from phenyl, p-fluorophenyl, m-fluorophenyl, p-hydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, m-methoxyphenyl, p-N,N-dimethylaminophenyl, m-N,N-dimethylaminophenyl, I^- p-$(CH_3)_3$-N^+-phenyl, I^- m-$(CH_3)_3$-N^+-phenyl, I^- m-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-phenyl, I^- p-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-phenyl, I^- m-(N,N-dimethylpiperazinium)-(N')-CH_2-$(OCH_2CH_2)_2$-O-phenyl, 3-methoxy-4-fluorophenyl, thienyl-2-yl, 5-cholorothienyl-2-yl, 3,4-difluorophenyl, I^- p-(N,N-dimethylpiperazinium)-(N')-CH_2-$(OCH_2CH_2)_2$-O-phenyl, 3-fluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3-pyridinyl, N-methyl-4-pyridinium, I^- N-methyl-3-pyridinium, 3,4-dioxymethylenephenyl, 3,4-dioxyethylenephenyl, and p-methoxycarbonylphenyl. Preferred compounds include 3-ethyl-3-butyl and 3-butyl-3-butyl compounds having each of the above preferred R^5 substituents in combination with the R^x substituents shown in Table 1. It is particularly preferred that one but not both of R^5 and R^6 is hydrogen.

It is especially preferred that R^4 and R^6 be hydrogen, that R^3 and R^5 not be hydrogen, and that R^3 and R^5 be oriented in the same direction relative to the plane of the molecule, i.e., both in α- or both in ß-configuration. It is further preferred that, where R^2 is butyl and R^1 is ethyl, then R^1 has the same orientation relative to the plane of the molecule as R^3 and R^5.

Set forth in Table 1A are lists of species of R^1/R^2, R^5/R^6 and R^x.

Table 1A: Alternative R Groups



R^1, R^2	R^3, R^4	R^5	$(R^x)q$
ethyl	HO-	Ph-	7-methyl
n-propyl	H-	p-F-Ph-	7-ethyl
n-butyl		m-F-Ph-	7-iso-propyl
n-pentyl		p-CH_3O-Ph-	7-tert-butyl
n-hexyl		p-CH_3O-Ph-	7-OH
iso-propyl		m-CH_3O-Ph-	7-OCH_3
iso-butyl		p-$(CH_3)_2N$-Ph-	7-O(iso-propyl)
iso-pentyl		m-$(CH_3)_2N$-Ph-	7-SCH_3
$CH_2C(=O)C_2H_5$		I^-, p-$(CH_3)_3$-N^+-Ph-	7-$SOCH_3$
$CH_2OC_2H_5$		I^-, m-$(CH_3)_3$-N^+-Ph-	7-SO_2CH_3
$CH_2CH(OH)C_2H_5$		I^-, p-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-SCH_2CH_3
CH_2O-(4-picoline)		I^-, m-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-NH_2
		I^-, p-(N,N-dimethylpiperazine)-(N')-CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-NHOH
		I^-, m-(N,N-dimethylpiperazine)-(N')-CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-$NHCH_3$
		m-F, p-CH_3O-Ph-	7-$N(CH_3)_2$
		3,4,dioxymethylene-Ph	7-$N^+(CH_3)_3$, I^-
		m-CH_3O-, p-F-Ph-	7-$NHC(=O)CH_3$
		4-pyridine	7-$N(CH_2CH_3)_2$
		N-methyl-4-pyridinium, I^-	7-$NMeCH_2CO_2H$
		3-pyridine	7-$N^+(Me)_2CH_2CO_2H$, I^-
		N-methyl-3-pyridinium, I^-	7-(N)-morpholine
		2-pyridine	7-(N)-azetidine
		p-CH_3O_2C-Ph-	7-(N)-N-methylazetidinium, I^-
		thienyl-2-yl	7-(N)-pyrrolidine
		5-Cl-thienyl-2-yl	7-(N)-N-methyl-pyrrolidinium, I^-
			7-(N)-N-methyl-morpholinium, I^-
			7-(N)-N'-methylpiperazine
			7-(N)-N'-dimethylpiperazinium, I^-
			7-NH-CBZ
			7-$NHC(O)C_5H_{11}$
			7-$NHC(O)CH_2Br$
			7-NH-C(NH)NH_2
			7-(2)-thiophene

continued next page...

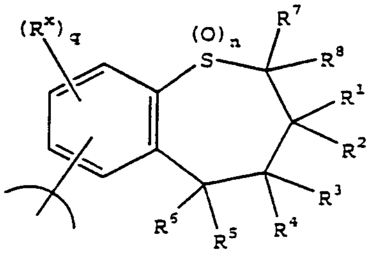
8-methyl
8-ethyl
8-iso-propyl
8-tert-butyl
8-OH
8-OCH_3
8-O(iso-propyl)
8-SCH_3
8-$SOCH_3$
8-SO_2CH_3
8-SCH_2CH_3
8-NH_2
8-NHOH
8-$NHCH_3$
8-$N(CH_3)_2$
8-$N^+(CH_3)_3$, I^-
8-$NHC(=O)CH_3$
8-$N(CH_2CH_3)_2$
8-$NMeCH_2CO_2H$
8-$N^+(Me)_2CH_2CO_2H$, I^-
8-(N)-morpholine
8-(N)-azetidine
8-(N)-N-methylazetidinium, I^-
8-(N)-pyrrolidine
8-(N)-N-methyl-pyrrolidinium, I^-
8-(N)-N-methyl-morpholinium, I^-
8-(N)-N'-methylpiperazine
8-(N)-N'-dimethylpiperazinium, I^-
8-NH-CBZ
8-$NHC(O)C_5H_{11}$
8-$NHC(O)CH_2Br$
8-$NH-C(NH)NH_2$
8-(2)-thiophene

continued next page...

9-methyl
9-ethyl
9-iso-propyl
9-tert-butyl
9-OH
9-OCH_3
9-O(iso-propyl)
9-SCH_3
9-$SOCH_3$
9-SO_2CH_3
9-SCH_2CH_3
9-NH_2
9-NHOH
9-$NHCH_3$
9-$N(CH_3)_2$
9-$N^+(CH_3)_3$, I^-
9-$NHC(=O)CH_3$
9-$N(CH_2CH_3)_2$
9-$NMeCH_2CO_2H$
9-$N^+(Me)_2CH_2CO_2H$, I^-
9-(N)-morpholine
9-(N)-azetidine
9-(N)-N-methylazetidinium, I^-
9-(N)-pyrrolidine
9-(N)-N-methyl-pyrrolidinium, I^-
9-(N)-N-methyl-morpholinium, I^-
9-(N)-N′-methylpiperazine
9-(N)-N′-dimethylpiperazinium, I^-
9-NH-CBZ
9-$NHC(O)C_5H_{11}$
9-$NHC(O)CH_2Br$
9-$NH-C(NH)NH_2$
9-(2)-thiophene

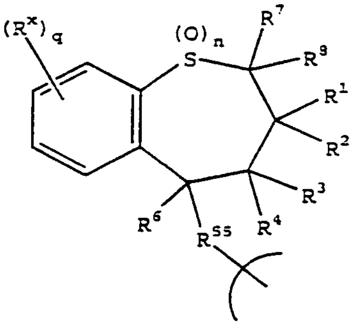
7-OCH_3, 8-OCH_3
7-SCH_3, 8-OCH_3
7-SCH_3, 8-SCH_3
6-OCH_3, 7-OCH_3, 8-OCH_3

Further preferred compounds of the present invention comprise a core structure having two or more pharmaceutically active benzothiepine structures as described above, covalently bonded to the core moiety via functional linkages. Such active benzothiepine structures preferably comprise:


(R^x)_q
(O)_n
S
R^7
R^8
R^1
R^2
R^3
R^4
R^5
R^6

(Formula DIV)

or:


(R^x)_q
(O)_n
S
R^7
R^8
R^1
R^2
R^3
R^4
R^55
R^6

(Formula DIVA)

where R^1, R^2, R^3, R^4, R^6, R^5, R^6, R^7, R^8, X, q and n are as defined above, and R^{55} is either a covalent bond or arylene.

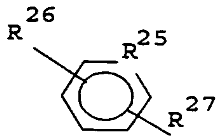
The core moiety can comprise alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR^7, $N^+R^7R^8$, S, SO, SO2, $S^+R^7R^8$, PR7, P+R7R8, phenylene, heterocycle, quatarnary heterocycle, quaternary heteroaryl, or aryl,

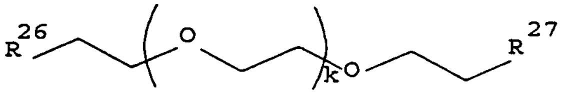
wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}$R15A-, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$;

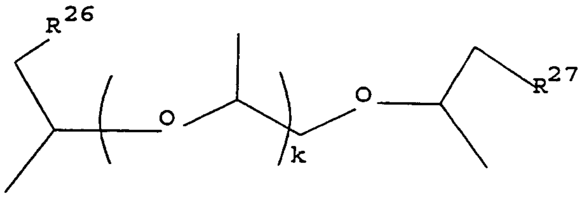
wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9$A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$, and

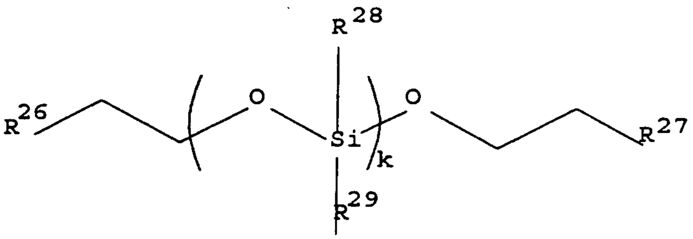
wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene.

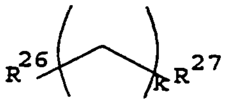
Exemplary core moieties include:







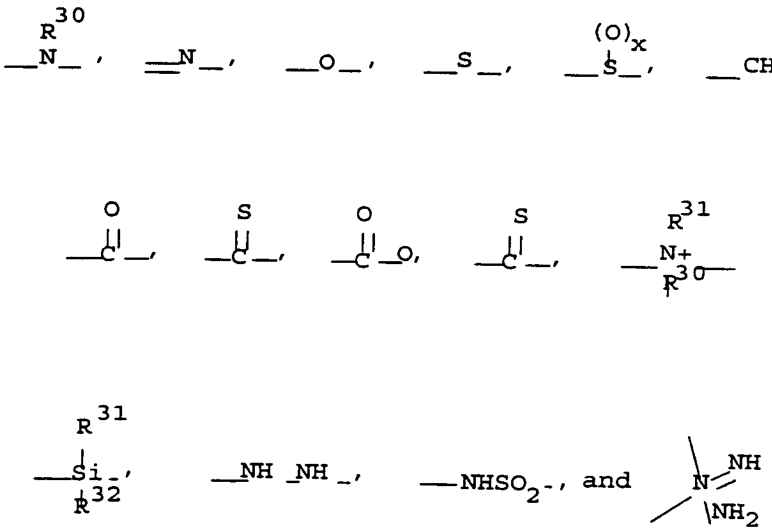

R28
R26
O
O
Si
k
R27
R29



wherein:

R^{25} is selected from the group consisting of C and N, and

R^{26} and R^{27} are independently selected from the group consisting of:



$-N(R^{30})-$, $=N-$, $-O-$, $-S-$, $-S(O)_x-$, $-CH_2-$

$-C(=O)-$, $-C(=S)-$, $-C(=O)O-$, $-C(=S)-$, $-N^{+}(R^{31})(R^{30})-$

$-Si(R^{31})(R^{32})-$, $-NH\,NH-$, $-NHSO_2-$, and $N(=NH)NH_2$

wherein R^{26}, R^{29}, R^{30} and R^{31} are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

A^{-} is a pharmaceutically acceptable anion, and k = 1 to 10.

In compounds of Formula DIV, R^{20}, R^{21}, R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII can be bonded at any of their 6-, 7-, 8-, or 9- positions to R^{19}. In compounds of Formula DIVA, it is preferred that

R^{55} comprises a phenylene moiety bonded at a m- or p-position thereof to R^{19}.

In another embodiment, a core moiety backbone, R^{19}, as discussed herein in Formulas DII and DIII can be multiply substituted with more than four pendant active benzothiepine units, i.e., R^{20}, R^{21}, R^{22}, and R^{23} as discussed above, through multiple functional groups within the core moiety backbone. The core moiety backbone unit, R^{19}, can comprise a single core moiety unit, multimers thereof, and multimeric mixtures of the different core moiety units discussed herein, i.e., alone or in combination. The number of individual core moiety backbone units can range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. The number of points of attachment of similar or different pendant active benzothiepine units within a single core moiety backbone unit can be in the range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. Such points of attachment can include bonds to C, S, O, N, or P within any of the groups encompassed by the definition of R^{19}.

The more preferred benzothiepine moieties comprising R^{20}, R^{21}, R^{22} and/or R^{23} conform to the preferred structures as outlined above for Formula I. The 3-carbon on each benzothiepine moiety can be achiral, and the substituents R^1, R^2, R^3, R^4, R^5 and R^x can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(exyalkylene) or oligo(oxyalkylene), especially poly- or oligo(exyethylene) or poly- or oligo(oxypropylene).

Dosages, Formulations, and Routes of Administration

The ileal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of action in the body, for example in the ileum of a mammal, e.g., a human.

For the prophylaxis or treatment of the conditions referred to above, the compounds of the present invention can be used as the compound *per se*.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, and alkaline earth salts such as magnesium and calcium salts.

The anions of the definition of A^- in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

The compounds of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

These compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

The amount of compound which is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

In general, a daily dose can be in the range of from about 0.3 to about 100 mg/kg bodyweight/day, preferably from about 1 mg to about 50 mg/kg bodyweight/day, more preferably from about 3 to about 10 mg/kg bodyweight/day. This total daily dose can be administered to the patient in a single dose, or in proportionate multiple subdoses. Subdoses can be administered 2 to 6 times per day. Doses can be in sustained release form effective to obtain desired results.

Orally administrable unit dose formulations, such as tablets or capsules, can contain, for example, from about 0.1 to about 100 mg of benzothiepine compound, preferably about 1 to about 75 mg of compound, more preferably from about 10 to about 50 mg of compound. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiepine ion derived from the salt.

Oral delivery of an ileal bile acid transport inhibitor of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

When administered intravenously, the dose can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

The solid dosage forms for oral administration including capsules, tablets, pills, powders, and granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Pharmaceutically acceptable carriers encompass all the foregoing and the like.

Treatment Regimen

The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

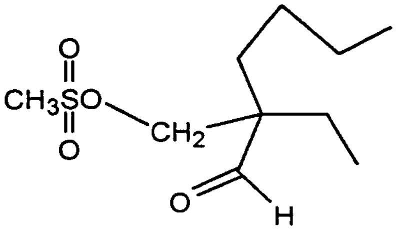
Initial treatment of a patient suffering from a hyperlipidemic condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic disease condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum cholesterol levels by any of the methods well known in the art, to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of compounds of the present invention are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of ileal bile acid transport inhibitor of the present invention which exhibits satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the hyperlipidemic condition.

The following non-limiting examples serve to illustrate various aspects of the present invention.

EXAMPLES OF SYNTHETIC PROCEDURES

Preparation 1

2-Ethyl-2-(mesyloxymethyl)hexanal (1)

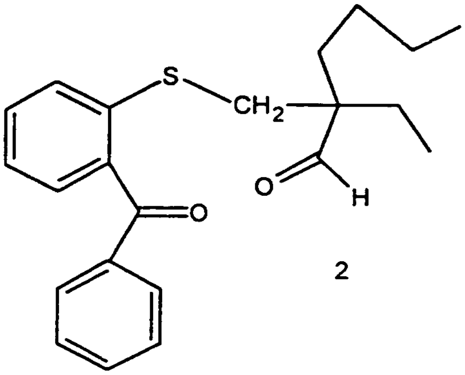


1

To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of triethylamine was added dropwise 15.8 g of 2-ethyl-2-(hydroxymethyl)hexanal, prepared according to the procedure described in Chem. Ber. **98**, 728-734 (1965), while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with dilute HCl and extracted with methlyene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give 24.4 g of brown oil.

Preparation 2

2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

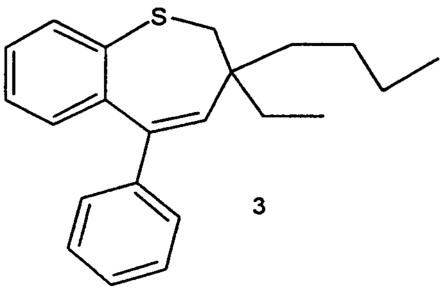


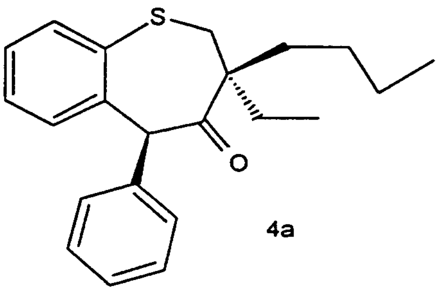
2

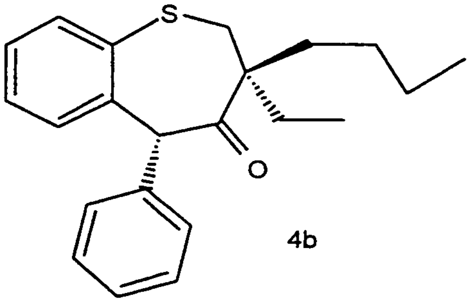
A mixture of 31 g (0.144 mol) of 2-mercaptobenzophenone, prepared according to the procedure described in WO 93/16055, 24.4 g (0.1 mole) of 2-ethyl-2-(mesyloxymethyl)-hexanal (**1**), 14.8 g (0.146 mole) of triethylamine, and 80 mL of 2-methoxyethyl ether was held at reflux for 24 h. The reaction mixture was poured into 3N HCl and extracted with 300 mL of methylene chloride. The methylene chloride layer was washed with 300 mL of 10% NaOH, dried over $MgSO_4$ and concentrated in vacuo to remove 2-methoxyethyl ether. The residue was purified by HPLC (10% EtOAc-hexane) to give 20.5 g (58%) of **2** as an oil.

Example 1

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine (3), *cis*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5*H*)4-one (4a) and *trans*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5*H*)4-one (4b)


3

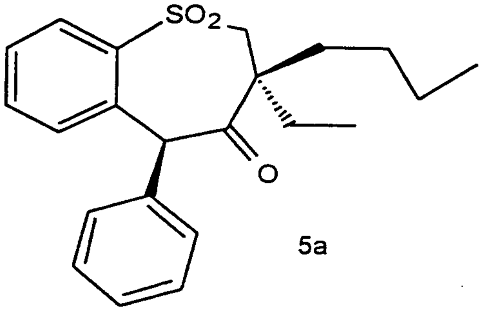

4a


4b

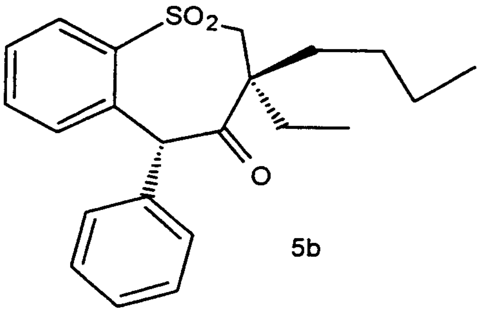
A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_3$ and 80 mL of anhydrous ethylene glycol dimethyl ether (DME) was held at reflux for 2 h. The reaction mixture was cooled to 5 °C. To the reaction mixture was added dropwise a solution of 3.54 g (0.01 mole) of **2** in 30 mL of DME in 40 min. The reaction mixture was stirred at room temperature for 16 h and then was held at reflux for 2 h and cooled before being poured into brine. The organic was extract into methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (hexane) to give 1.7 g (43%) of **3** as an oil in the first fraction. The second fraction was discarded and the third fraction was further purified by HPLC (hexane) to give 0.07 g (2%) of **4a** in the earlier fraction and 0.1 g (3%) of **4b** in the later fraction.

Example 2

***cis*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5*H*)4-one-1,1-dioxide (5a) and *trans*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5*H*)4-one-1,1-dioxide (5b)**



5a



5b

To a solution of 1.2 g (3.5 mmole) of 50-60% MCPBA in 20 mL of methylene chloride was added 0.59 g (1.75 mmole) of a mixture of **4a** and **4b** in 10 mL of methylene chloride. The reaction mixture was stirred for 20 h. An additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added and the reaction mixture was stirred for an additional 3 h then was triturated with 50 mL of 10% NaOH. The insoluble solid was filtered. The methylene chloride layer of the filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual syrup was purified by HPLC (5% EtOAc-hexane) to give 0.2 g (30%)of **5a** as an oil in the first fraction and 0.17 g (26%) of **5b** as an oil in the second fraction.

Example 3

(3α,4α,5β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-

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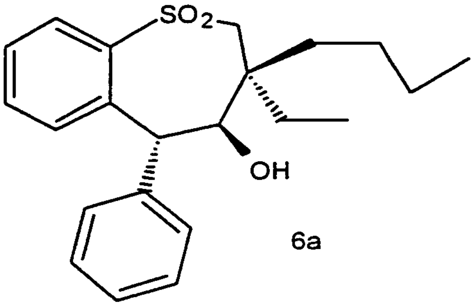
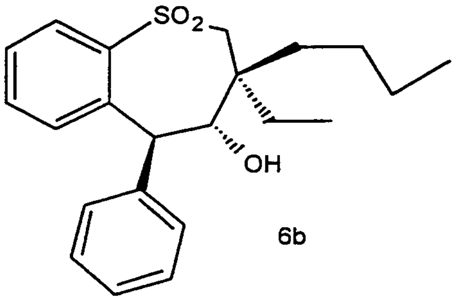
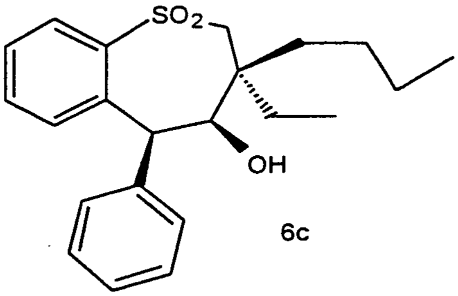
tetrahydrobenzothiepine-1,1-dioxide (6a), (3α,4β,5α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6b), (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)



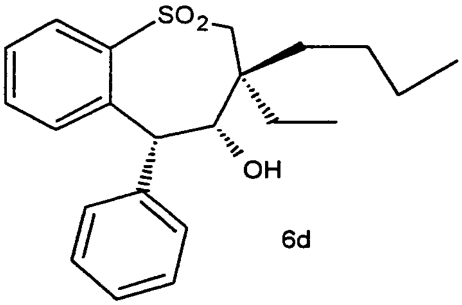
6a



6b



6c



6d

A. Reduction of 5a and 5b with Sodium Borohydride

To a solution of 0.22 g (0.59 mmole) of **5b** in 10 mL of ethanol was added 0.24 g (6.4 mmole) of sodium borohydride. The reaction mixture was stirred at room temperature for 18 h and concentrated in vacuo to remove ethanol. The residue was triturated with water and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give 0.2 g of syrup. In a separate experiment, 0.45 g of **5a** was treated with 0.44 g of sodium borohydride in 10 mL of ethanol and was worked up as described above to give 0.5 g of syrup which was identical to the 0.2 g of syrup obtained above. These two materials were combined and purified by HPLC using 10% EtOAc-hexane as eluant. The first fraction was 0.18 g (27%) of **6a** as a syrup. The second fraction was 0.2 g (30%) of **6b** also as a syrup. The column was then eluted with 20% EtOAc-hexane to give 0.077 g (11%) of **6c** in the third fraction as a solid. Recrystallization from hexane gave a solid, mp 179-181 °C. Finally, the column was eluted with 30% EtOAc-hexane to give 0.08 g (12%) of **6d** in the fourth fraction as a solid. Recrystallization from hexane gave a solid, mp 160-161 °C.

B. Conversion of 6a to 6c and 6d with NaOH and PTC

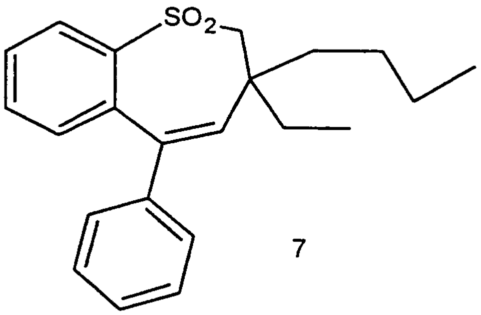
To a solution of 0.29 g (0.73 mmole) of **6a** in 10 mL CH_2Cl_2 , was added 9 g of 40% NaOH. The reaction mixture was stirred for 0.5 h at room temperature and was added one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst (PTC). The mixture was stirred for 0.5 h at room temperature before being treated with 25 mL of ice-crystals then was extracted with CH_2Cl_2 (3x10 ml), dried over $MgSO_4$ and concentrated in vacuo to recover 0.17 g of a colorless film. The components of this mixture were separated using an HPLC and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2-(2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the first fraction, 30.9 mg (11%) of **6c** in the second fraction and 90.0 mg (31%) of **6d** in the third fraction.

Oxidation of 6a to 5b

To a solution of 0.20 g (0.52 mmole) of **6a** in 5 mL of CH_2Cl_2 was added 0.23 g (1.0 mmole) of pyridinium chlorochromate. The reaction mixture was stirred for 2 h then was treated with additional 0.23 g of pyridinium chlorochromate and stirred overnight. The dark reaction mixture was poured into a ceramic filterfrit containing silica gel and was eluted with CH_2Cl_2. The filtrate was concentrated in vacuo to recover 167 mg (87%) of **5b** as a colorless oil.

Example 4

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-dioxide (7)

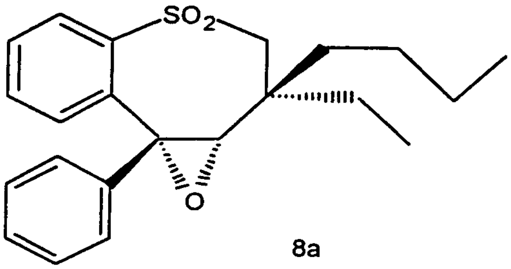


7

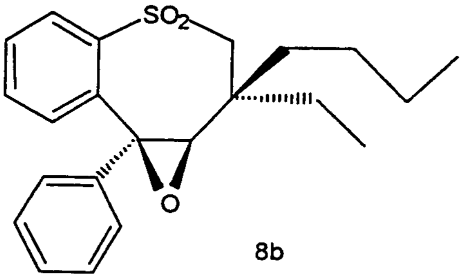
To a solution of 5.13 g (15.9 mmole) of **3** in 50 mL of CH_2Cl_2 was added 10 g (31.9 mmole)of 50-60% MCPBA (m-chloroperoxybenzoic acid) portionwise causing a mild reflux and formation of a white solid. The reaction mixture was allowed to stir overnight under N_2 and was triturated with 25 mL of water followed by 50 mL of 10% NaOH solution. The organic was extracted into CH_2Cl_2 (4x20 mL). The CH_2Cl_2 extract was dried over $MgSO_4$ and evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

Example 5

(1aα,2β,8bα) 2-Butyl-2-ethyl-8b-phenyl-1α,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (8a)
(1aα,2α,8bα) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (8b)



8a



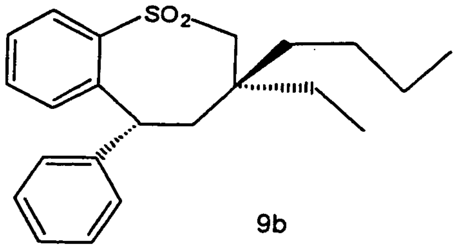
8b

To 1.3 g (4.03 mole) of **3** in 25 mL of $CHCl_3$ was added portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a mild exotherm. The reaction mixture was stirred under N_2 overnight and was then held at reflux for 3 h. The insoluble white slurry was filtered. The filtrate was extracted with 10% potassium carbonate (3x50 mL), once with brine, dried over $MgSO_4$, and concentrated in vacuo to give 1.37 g of a light yellow oil. Purification by HPLC gave 0.65 g of crystalline product. This product is a mixture of two isomers. Trituration of this crystalline product in hexane recovered 141.7 mg (10%) of a white crystalline product. This isomer was characterized by NMR and mass spectra to be the (1aα,2β,8bα) isomer **8a**. The hexane filtrate was concentrated in vacuo to give 206 mg of white film which is a mixture of 30% **8a** and 70% **8b** by ^1H NMR.

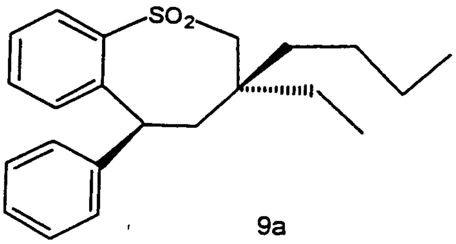
Example 6

cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (9a), trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (9b), and 3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidine-2,3,4,5-

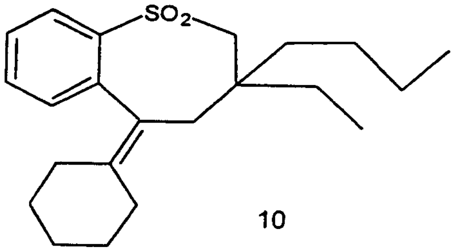
tetrahydrobenzothiepine-1,1-dioxide (10)



9b



9a



10

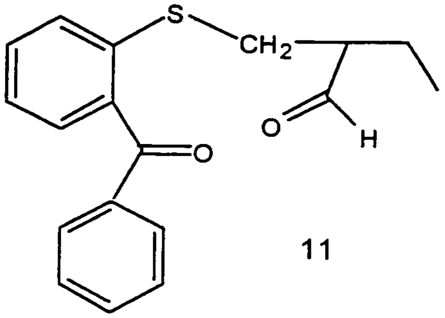
A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of **8a** and **8b** was dissolved in 15 ml MeOH in a 3 oz. Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C catalyst. This mixture was hydrogenated at 70 psi H_2 for 5 h and filtered. The filtrate was evaporated to dryness in vacuo to recover 0.117 g of a colorless oil. This material was purified by HPLC eluting with EtOAc-hexane. The first fraction was 4.2 mg (3%) of **9b**. The second fraction, 5.0 mg (4%), was a 50/50 mixture of **9a** and **9b**. The third fraction was 8.8 mg (6%) of **6a** . The fourth fraction was 25.5 mg (18%) of **6b**. The fifth fraction was 9.6 mg (7%) of a mixture of **6b** and a product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide based on mass spectrum. The sixth fraction was 7.5 mg (5%) of a mixture of **6d** and one of the isomers of **10**, **10a**.

Example 7

In another experiment, a product (3.7 g) from epoxidation of **3** with excess MCPBA in refluxing $CHCl_3$ under air was hydrogenated in 100 mL of methanol using 1 g of 10% Pd/C catalyst and 70 psi hydrogen. The product was purified by HPLC to give 0.9 g (25%) of **9b**, 0.45 g (13%) of **9a**, 0.27 g (7%) of **6a**, 0.51 g (14%) of **6b**, 0.02 g (1%) of **6c**, 0.06 g (2%) of one isomer of **10**, **10a** and 0.03 g (1%) of another isomer of **10**, **10b**.

Example 8

2-((2-Benzoylphenylthio)methyl)butyraldehyde (11)

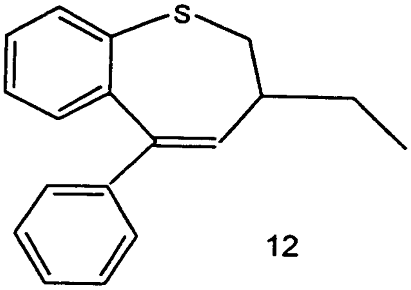


11

To an ice bath cooled solution of 9.76 g (0.116 mole) of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g (0.116 mole) of 2-mercaptobenzophenone in 40 mL of THF followed by 13 g (0.128 mole) of triethylamine. The reaction mixture was stirred at room temperature for 3 days , diluted with ether, and was washed successively with dilute HCl, brine, and 1 M potassium carbonate. The ether layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc-hexane) to give 22 g (64%) of **11** in the second fraction. An attempt to further purifiy this material by kugelrohr distillation at 0.5 torr (160-190 °C) gave a fraction (12.2 g) which contained starting material indicating a reversed reaction during distillation. This material was dissolved in ether (100 mL) and was washed with 50 mL of 1 M potassium carbonate three times to give 6.0 g of a syrup which was purified by HPLC (10% EtOAc-hexane) to give 5.6 g of pure **11**.

Example 9

3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine (12)

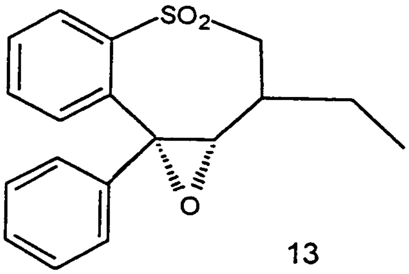


12

To a mixture of 2.61 g (0.04 mole) of zinc dust and 60 mL of DME was added 7.5 g (0.048 mole) of $TiCl_3$. The reaction mixture was held at reflux for 2 h. A solution of 2.98 g (0.01 mole) of **11** was added dropwise in 1 h. The reaction mixture was held at reflux for 18 h, cooled and poured into water. The organic was extracted into ether. The ether layer was washed with brine and filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated. The residual oil (2.5 g) was purified by HPLC to give 2.06 g (77%) of **12** as an oil in the second fraction.

Example 10

(1aα,2α,8bα) 2-Ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino-[4,5-*b*]oxirene-4,4-dioxide (13)

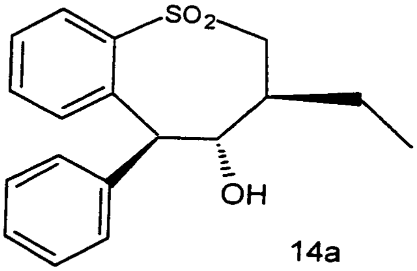


13

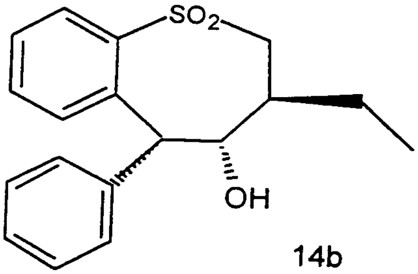
To a solution of 1.5 g (5.64 mmole) of **12** in 25 ml of $CHCl_3$ was added 6.8 g (19.4 mmole) of 50-60% MCPB portionwise causing an exothem and formation of a white solid. The mixture was stirred at room temperature overnight diluted with 100 ml methylene chloride and washed successively with 10% K_2CO_3 (4x50 ml), water (twice with 25 ml) and brine. The organic layer was then dried over $MgSO_4$ and evaporated to dryness to recover 1.47 g of an off white solid. ^1H NMR indicated that only one isomer is present. This solid was slurried in 200 ml of warm Et_2O and filtered to give 0.82 g (46%) of **13** as a white solid, mp 185-186.5 °C.

Example 11

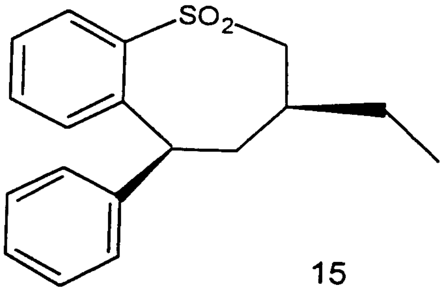
(3α,4β,5α)- 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (14a), (3α,4β,5β) 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (14b), and cis-3-Ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (15)



14a



14b

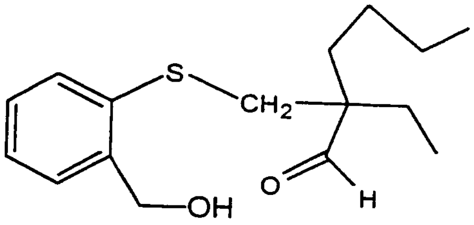


15

A mixture of 0.5 g (1.6 mole) of **13**, 50 ml of acetic acid and 0.5 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 4 h. The crude reaction slurry was filtered and the filtrate was stirred with 150 ml of a saturated $NaHCO_3$ solution followed by 89 g of $NaHCO_3$ powder portionwise to neutralize the rest of acetic acid. The mixture was extracted with methylene chloride (4x25 ml), then the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 0.44 g (87%) of a voluminous white solid which was purified by HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of **15** in the first fraction, 272 mg (54%) of **14a** as a solid, mp 142-143.5 °C, in the second fraction, and 35 mg (7%) of impure **14b** in the third fraction.

Example 12

2-Ethyl-2-((2-Hydroxymethylphenyl)thiomethyl)hexenal (16)



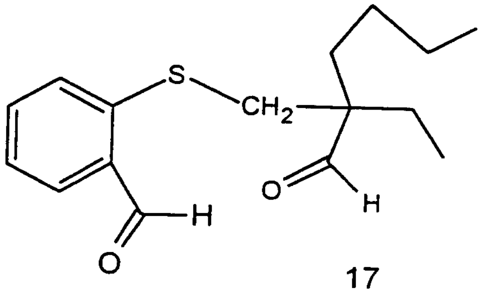
16

A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl alcohol, 6.4 g (0.032 mole) of **1**, 3.6 g (0.036 mole) of triethylamine and 25 mL of 2-methoxyethyl ether was held at reflux for 7 h. Additional 1.1 g of mercaptobenzyl alcohol and 0.72 g of triethylamine was added to the reaction mixture and the mixture was held at reflux for additional 16 h. The reaction mixture was cooled and poured into 6N HCl and extracted with methylene chloride. The methylene chloride extract was washed twice with 10% NaOH, dried over $MgSO_4$ and concentrated in vacuo to give 9.6 g of residue. Purification by HPLC (20% EtOAc-hexane) gave 3.7 g

(41%)of **16** as an oil.

Example 13

2-Ethyl-2-((2-formylphenyl)thiomethyl)hexenal (17)

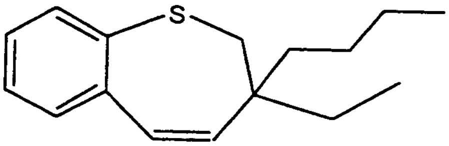


17

A mixture of 3.7 g of **16**, 5.6 g (0.026 mole) of pyridinium chlorochromate, 2 g of Celite and 30 mL of methylene chloride was stirred for 18 h and filtered through a bed of silica gel. The silica gel was eluted with methylene chloride. The combined methylene chloride eluant was purified by HPLC (20% ETOAc-hexane) to give 2.4 g (66%) of an oil.

Example 14

3-Butyl-3-ethyl-2,3-dihydrobenzothiepine (18)

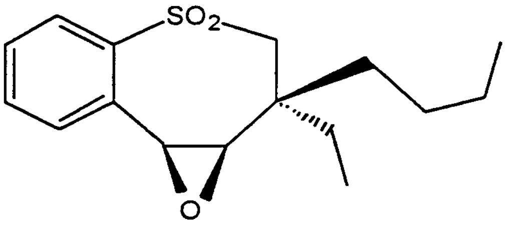


18

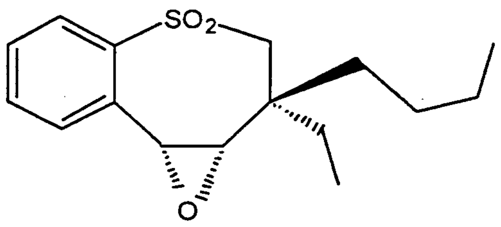
A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_3$, and 50 mL of DME was held at reflux for 2 h and cooled to room temperature. To this mixture was added 2.4 g (8.6 mmole) of **17** in 20 mL of DME in 10 min. The reaction mixture was stirred at room temperature for 2 h and held at reflux for 1 h then was let standing at room temperature over weekend. The reaction mixture was poured into dilute HCl and was stirred with methylene chloride. The methylene chloride-water mixture was filtered through Celite. The methylene chloride layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 3.0 g of a residue. Purification by HPLC gave 0.41 g (20%) of **18** as an oil in the early fraction.

Example 15

(1aα,2α,8bα) 2-Butyl-2-ethyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (19a) and (1aα,2β,8bα) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (19b)



19a

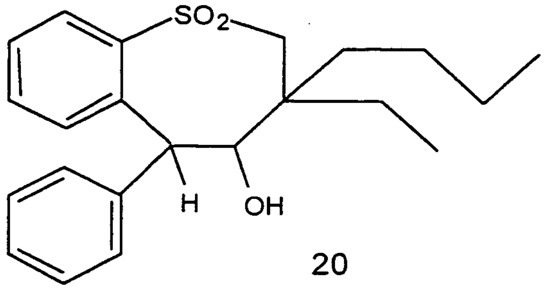


19b

To a solution of 0.4 g of 0.4 g (1.6 mmole) of **18** in 30 mL of methylene chloride was added 2.2 g (3.2 mmole) of 50-60% MCPBA. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was dissolved in 30 mL of $CHCl_3$ and was held at reflux for 18 h under N_2. The reaction mixture was stirred with 100 mL of 10% NaOH and 5 g of sodium sulfite. The methylene chloride layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (20% EtOAc-hexane) to give a third fraction which was further purified by HPLC (10% EtOAc-hexane) to give 0.12 g of syrup in the first fraction. Recrystallization from hexane gave 0.08 g (17%) of **19a**, mp 89.5-105.5 °C. The mother liquor from the first fraction was combined with the second fraction and was further purified by HPLC to give additional **19a** in the first fraction and 60 mg of **19b** in the second fraction. Crystallization from hexane gave 56 mg of a white solid.

Example 16

3-Butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (20)

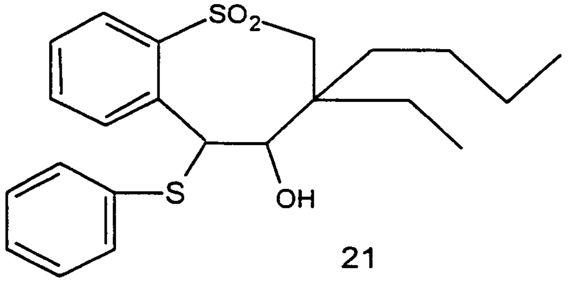


20

This product was isolated along with **6b** from hydrogenation of a mixture of **8a** and **8b**.

Example 17

3-Butyl-3-ethyl-4-hydroxy-5-phenylthio-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (21)



21

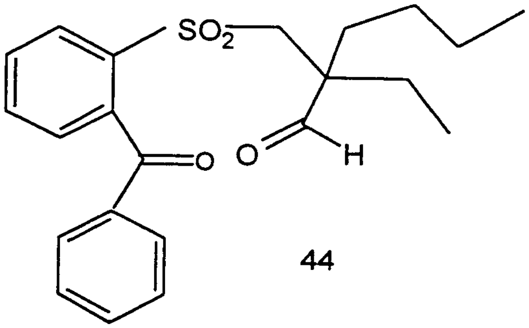
A mixture of 25 mg (0.085 mmole) of **19b**, 0.27 g (2.7 mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium carbonate, and 4 mL of DMF was stirred at room temperature under N_2 for 19 h. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed successively with 10% NaOH and brine, dried over $MgSO_4$, and concentrated in vacuo to give 0.19 g of semisolid which contain substantial amounts of diphenyl disulfide. This material was purified by HPLC (5% EtOAc-hexane) to remove diphenyl disulfide in the first fraction. The column was then eluted with 20% EtOAc-hexane to give 17 mg of a first fraction, 4 mg of a second fraction and 11 mg of a third fraction which were three different isomers of **21**, i.e. **21a**, **21b**, and **21c**, respectively, by ^1H NMR and mass spectra.

Example 18

Alternative Synthesis of 6c and 6d

A. Preparation from 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

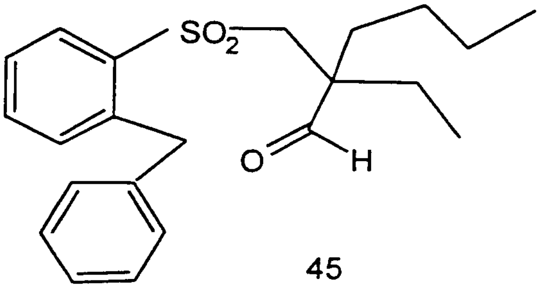
Step 1. 2-((2-Benzoylphenylsulfonyl)methyl)-2-ethylhexanal (44)



44

To a solution of 9.0 g (0.025 mole) of compound **2** in 100 ml of methylene chloride was added 14.6 g (0.025 mol) of 50-60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h then was stirred with 200 ml of 1 M potassium carbonate and filtered through Celite. The methylene chloride layer was washed twice with 300 ml of 1 M potassium carbonate, once with 10% sodium hydroxide and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene chloride solution was dried and concentrated in vacuo to give 9.2 g (95%)of semisolid. A portion (2.6 g) of this solid was purified by HPLC(10% ethyl acetate-hexane) to give 1.9 g of crystals, mp 135-136 °C

Step 2. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



45

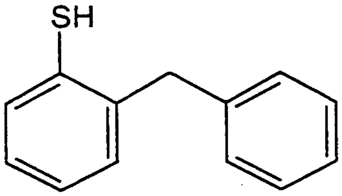
A solution of 50 g (0.13 mole) of crude **44** in 250 ml of methylene chloride was divided in two portions and charged to two Fisher-Porter bottles. To each bottle was charged 125 ml of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time but only 1 g of Pd/C was charged to the reaction mixture. The combined reaction mixture was filtered and concentrated in vacuo to give 46.8 g of **45** as brown oil.

Step 3. (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)

To a solution of 27.3 g (73.4 mmole) of **45** in 300 ml of anhydrous THF cooled to 2 °C with an ice bath was added 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred for 20 min, quenched with 300 ml of 10% HCl and extracted with methylene chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give 24.7 g of yellow oil. Purification by HPLC (ethyl acetate-hexane) yielded 9.4 g of recovered **45** in the first fraction, 5.5 g (20%) of **6c** in the second fraction and 6.5 g (24%) of **6d** in the third fraction.

B. Preparation from 2-hydroxydiphenylmethane

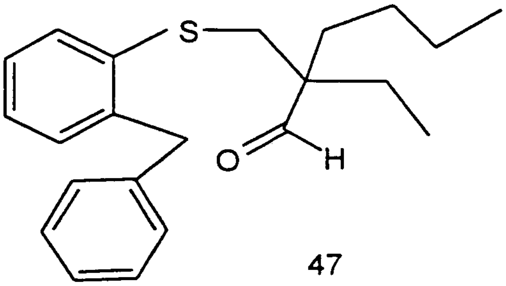
Step 1. 2-mercaptodiphenylmethane (46)



46

To a 500 ml flask was charged 16 g (0.33 mol) of 60% sodium hydride oil dispersion. The sodium hydride was washed twice with 50 ml of hexane. To the reaction flask was charged 100 ml of DMF. To this mixture was added a solution of 55.2 g (0.3 mol) of 2-hydroxydiphenylmethane in 200 ml of DMF in 1 h while temperature was maintained below 30 °C by an ice-water bath. After complete addition of the reagent, the mixture was stirred at room temperature for 30 min then cooled with an ice bath. To the reaction mixture was added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl chloride at once. The ice bath was removed and the reaction mixture was stirred at room temperature for 18 h before being poured into 300 ml of water. The organic was extracted into 500 ml of toluene. The toluene layer was washed successively with 10% sodium hydroxide and brine and was concentrated in vacuo to give 78.6 g of a yellow oil which was 95% pure dimethyl *O*-2-benzylphenyl thiocarbamate. This oil was heated at 280-300 °C in a kugelrohhr pot under house vacuum for 30 min. The residue was kugelrohr distilled at 1 torr (180-280 °C). The distillate (56.3 g) was crystallized from methanol to give 37.3 g (46%) of the rearranged product dimethyl *S*-2-benzylphenyl thiocarbamate as a yellow solid. A mixture of 57 g (0.21 mole) of this yellow solid, 30 g of potassium hydroxide and 150 ml of methanol was stirred overnight then was concentrated in vacuo. The residue was diluted with 200 ml of water and extracted with ether. The aqueous layer was made acidic with concentrate HCl, The oily suspension was extracted into ether. The ether extract was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of 2-mercaptodiphenylmethane as a yellow solid.

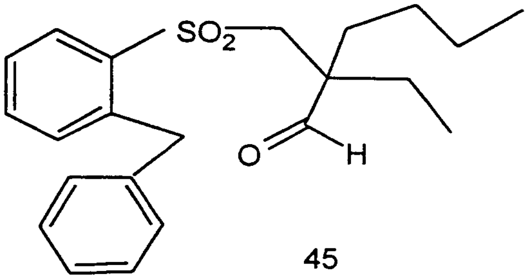
Step 2. 2-((2-Benzylphenylthio)methyl)-2-ethylhexanal (47)



47

A mixture of 60 g (03 mole) of yellow solid from step 1, 70 g (0.3 mole) of compound **1** from preparation 1, 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-methoxyethyl ether was held at reflux for 6 hr and concentrated in vacuo. The residue was triturated with 500 ml of water and 30 ml of concentrate HCl. The organic was extracted into 400 ml of ether. The ether layer was washed successively with brine, 10% sodium hydroxide and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2-5% ethyl acetate-hexane as eluent to give 2-((2-benzylphenylthio)methyl)-2-ethylhexanal **47** as a yellow syrup.

Step 3. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



45

To a solution of 72.8 g (0.21 mole) of yellow syrup from step 2 in 1 liter of methylene chloride cooled to 10 °C was added 132 g of 50-60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50-60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered through Celite. The methylene chloride solution was washed twice with 1 liter of 1 M potassium carbonate then with 1 liter of brine. The methylene chloride layer was dried over magnesium sulfate and concentrated to 76 g of 2-((2-benzylphenylsulfonyl)methyl)-2-ethylhexanal **45** as a syrup.

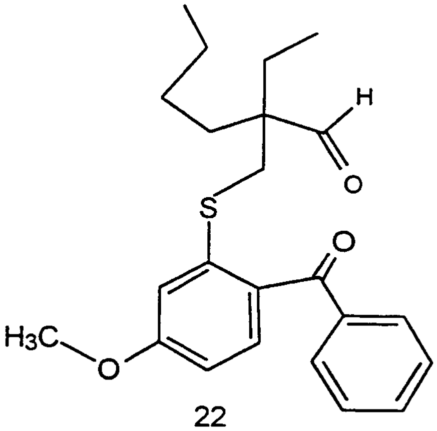
Step 4. (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)

Reaction of **45** with potassium t-butoxide according to the procedure in step 3 of procedure A gave pure **6c** and **6d** after HPLC.

Example 19

(3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26)

Step 1. Preparation of 2-((2-benzoyl-4-methoxy phenylthio)methyl)-2-ethylhexanal (22)



22

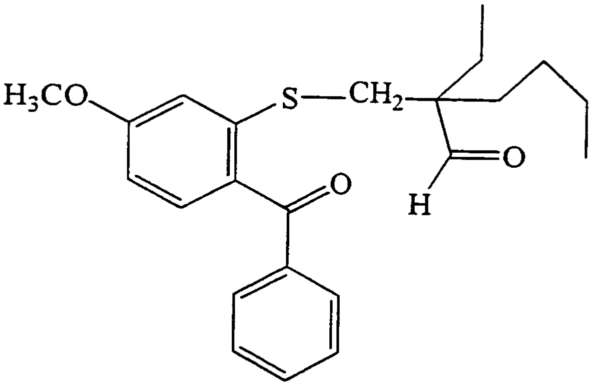
2-Hydroxy-4-methoxybenzophenone was converted to the dimethyl *O*-2-benzoyphenyl thiocarbamate by methods previously described in example 18. The product can be isolated by recrystallization from ethanol. Using this improved isolation procedure no chromatography was needed. The thermal rearrangement was performed by reacting the thiocarbamate(5 g) in diphenyl ether at 260 °C as previously described. The improved isolation procedure which avoided a chromatography step was described below.

The crude pyrolysis product was then heated at 65 °C in

100 ml of methanol and 100 ml of THF in the presence of 3.5 g of KOH for 4 h. After removing THF and methanol by rotary evaporation the solution was extracted with 5 % NaOH and ether. The base layer was acidified and extracted with ether to obtain a 2.9 g of crude thiophenol product. The product was further purified by titrating the desired mercaptan into base with limited KOH. After acidification and extraction with ether pure 2-mercapto-4-methoxybenzophenone (2.3 g) was isolated.

2-mercapto-4-methoxybenzophenone can readily be converted to the 2-((2-benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (**22**) by reaction with 2-ethyl-2-(mesyloxymethyl)hexanal (**1**) as previously described.

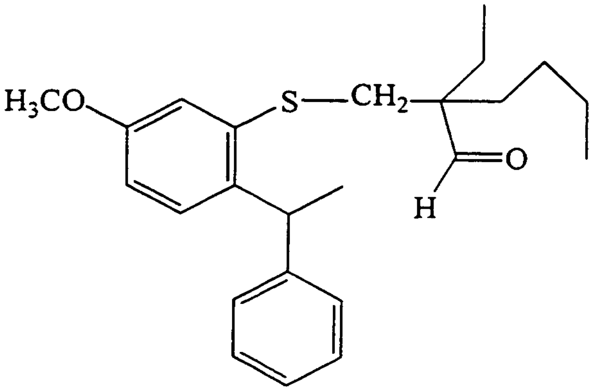
Step 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (23)



23

Substrate **22** was readily oxidized to **2-((2-benzoyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (23)** as described in example 18.

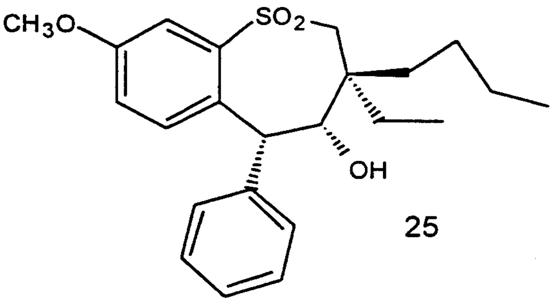
Step 3. 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (24)



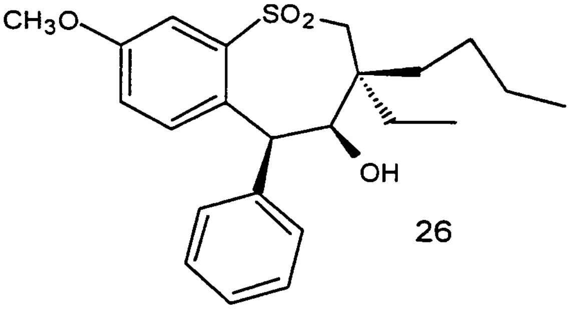
24

Sulfone **23** was then reduced to **2-((2-benzyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (24)** as described in example 18.

Step 4. (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26)



25



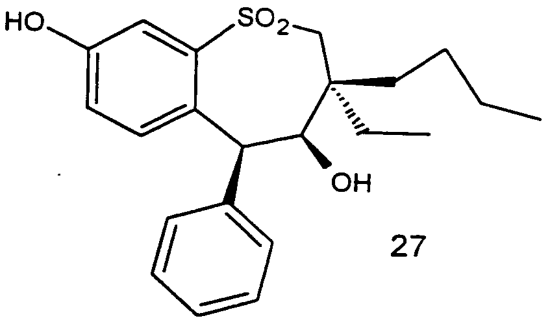
26

A 3-neck flask equipped with a powder addition funnel,thermocouple and nitrogen bubbler was charged with 19.8 g (0.05 mole) of sulfone **24** in 100 ml dry THF. The reaction was cooled to -1.6 °C internal temperature by means of ice/salt bath. Slowly add 5.61 g (0.05 mole) of potassium t-butoxide by means of the powder addition funnel. The resulting light yellow solution was maintained at -1.6 °C. After 30 min reaction 400 ml of cold ether was added and this solution was extracted with cold 10 % HCl. The acid layer was extracted with 300 ml of methylene chloride. The organic layers were combined and dried over magnesium sulfate and after filtration stripped to dryness to obtain 19.9 g of product. ^{1}H nmr and glpc indicated a 96% conversion to a 50/50 mixture of **25** and **26**. The only other observable compound was 4% starting sulfone **24**.

The product was then dissolved in 250 ml of 90/10 hexane/ethyl acetate by warming to 50 °C. The solution was allowed to cool to room temperature and in this way pure **26** can be isolated. The crystallization can be enhanced by addition of a seed crystal of **26**. After 2 crystallizations the mother liquor which was now 85.4% **25** and has a dry weight of 8.7 g. This material was dissolved in 100 ml of 90/10 hexane/ethyl acetate and 10 ml of pure ethyl acetate at 40 C. Pure **25** can be isolated by seeding this solution with a seed crystal of **25** after storing it overnight at 0 C.

Example 20

(3α,4α,5α) 3-Butyl-3-ethyl-4,8-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (27)



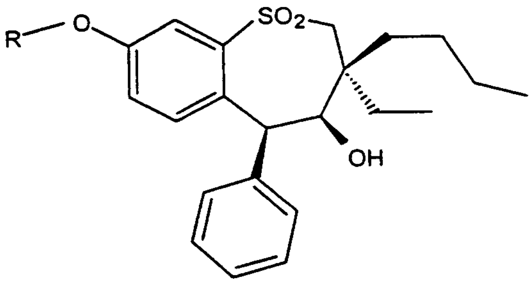
27

In a 25 ml round bottomed flask, 1 g of **26**(2.5 mmoles) and 10 ml methylene chloride were cooled to - 78 °C with stirring. Next 0.7 ml of boron tribromide(7.5 mmole) was added via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 6 h. The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water.The organic layer was dried over magnesium sulfate. The product (0.88g) **27** was characterized by NMR and mass spectra.

Example 21

General Alkylation of phenol 27

A 25 ml flask was charged with 0.15 g of **27**(0.38 mmole), 5 ml anhydrous DMF, 54 mg of potassium carbonate(0.38 mmole) and 140 mg ethyl iodide (0.9 mmole). The reaction was stirred at room temperature overnight.The reaction was diluted with 50 ml ethyl ether and washed with water (25 ml) then 5% NaOH (20 ml) and then sat. NaCl. After stripping off the solvent the ethoxylated product **28** was obtained in high yield. The product was characterized by NMR and mass spectra. This same procedure was used to prepare products listed in table 1 from the corresponding iodides or bromides. For higher boiling alkyl iodides and bromides only one equivalent of the alkyl halide was used.



Formula for Table 1

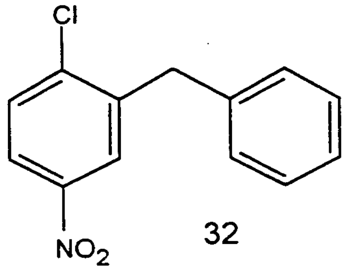
Table 1

Compound No.	**R**
27	H
26	Me
28	Et
29	hexyl
30	Ac
31	(CH2)6-N-pthalimide

Example 22

(3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (37) and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (38)

Step 1. Preparation of 2-chloro-5-nitrodiphenylmethane (32)

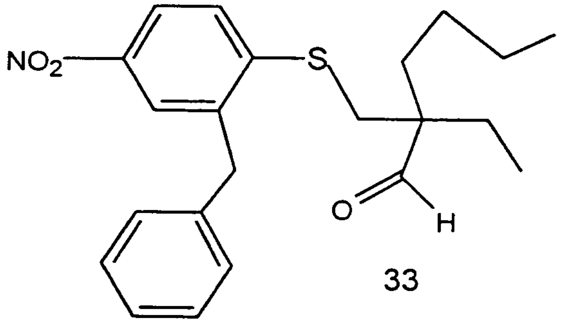


32

Procedure adapted from reference :Synthesis -Stuttgart 9 770-772 (1986) Olah G. Et al

Under nitrogen, a 3 neck flask was charged with 45 g (0.172 mole) of 2-chloro-5-nitrobenzophenone in 345 ml methylene chloride and the solution was cooled to ice/water temperature. By means of an additional funnel, 150 g(0.172 mole) of trifluoromethane sulfonic acid in 345 ml methylene chloride was added slowly. Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride was added dropwise to the chilled solution. Both addition steps(trifluoromethane sulfonic acid and triethylsilane)were repeated. After the additions were completed the reaction was allowed to slowly warm up to room temperature and stirred for 12 h under nitrogen. The reaction mixture was then poured into a chilled stirred solution of 1600 ml of saturated sodium bicarbonate. Gas evolution occurred. Poured into a 4 liter separatory funnel and separated layers. The methylene chloride layer was isolated and combined with two 500 ml methylene chloride extractions of the aqueous layer. The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give 39 g product. Structure **32** was confirmed by mass spectra and proton and carbon NMR.

Step 2. Preparation of 2-((2-benzyl-4-nitrophenylthio)methyl)-2-ethylhexanal (33)

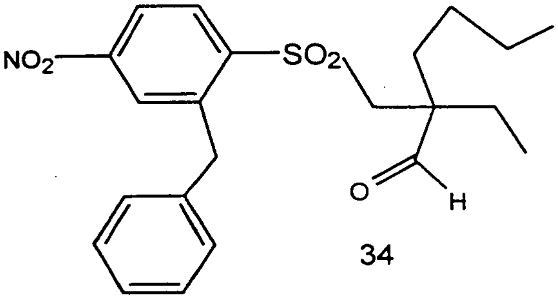


33

The 2-chloro-5-nitrodiphenylmethane product **32** (40 g, 0.156 mole) from above was placed in a 2 liter 2 neck flask with water condenser. Next 150 ml DMSO and 7.18 g (0.156 mole) of lithium sulfide was added and the solution was stirred at 75 °C for 12 h. The reaction was cooled to room temperature and then 51.7 g of mesylate IV was added in 90 ml DMSO. The reaction mixture was heated to 80 °C under nitrogen. After 12 h monitored by TLC and added more mysylate if necessary.

Continued the reaction until the reaction was completed. Next the reaction mixture was slowly poured into a 1900 ml of 5% acetic aqueous solution with stirring, extracted with 4 X 700 ml of ether, and dried over MgSO4. After removal of ether, 82.7 g of product was isolated. The material can be further purified by silica gel chromatography using 95% hexane and 5 % ethyl acetate. If pure mysylate was used in this step there was no need for further purification. The product **33** was characterized by mass spectra and NMR.

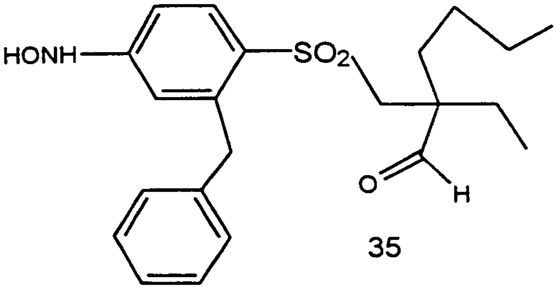
Step 3. Oxidation of the nitro product 33 to the sulfone 2-((2-benzyl-4-nitrophenylsulfonyl)methyl)-2-ethylhexanal (34)



34

The procedure used to oxidize the sulfide **33** to the sulfone **34** has been previously described.

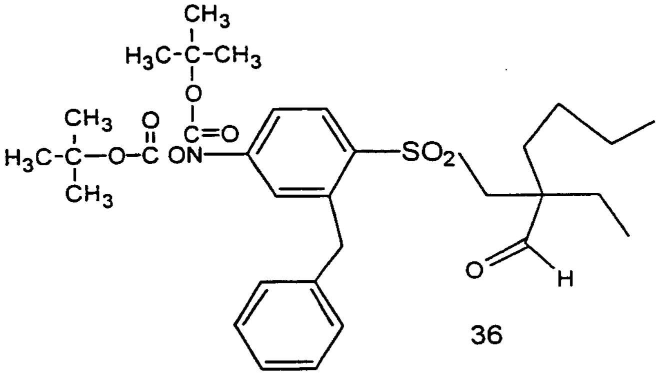
Step 4. Reduction of 34 to 2-((2-benzyl-4-hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (35)



35

A 15 g sample of **34** was dissolved in 230 ml of ethanol and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt.% Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate **34** was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product **35** was isolated by filtering off the Pd/C and then stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

Step 5. Preparation of the 2-((2-benzyl-4-*N,O*-di-(t-butoxy-carbonyl)hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (36).



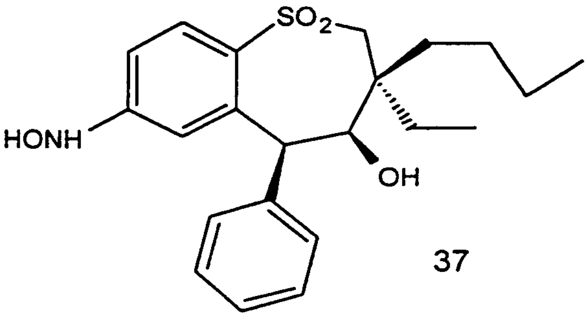
36

A 13.35 g sample of **35** (0.0344 mole) in 40 ml of dry THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of di-t-butyl dicarbonate in 7 ml THF. Heated at 60 °C overnight. Striped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.

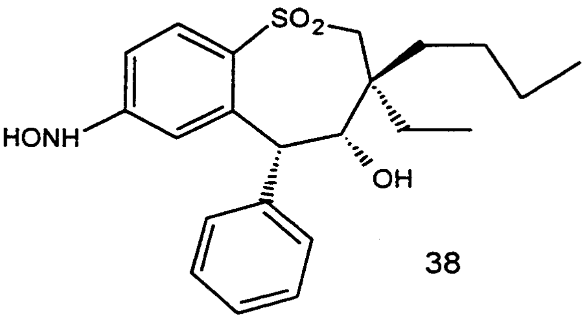
The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product **36** was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.

Step 6. (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-

1,1-dioxide (37) and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (38)



37



38

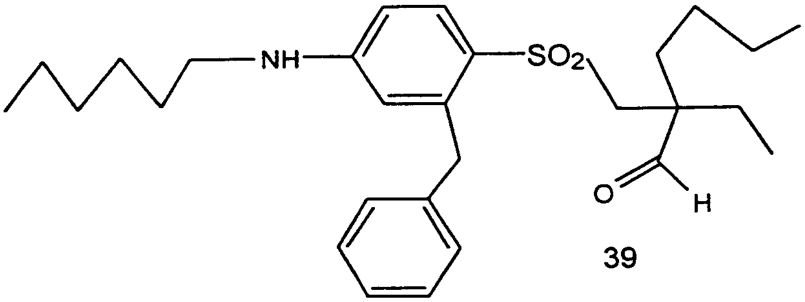
A 250ml 3-neck round bottomed flask was charged with 4 g of **36** (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78 °C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide(20.4 mmoles) with stirring and maintaining a -78 °C reaction temperature. After 1 h at -78 °C the addition of base was completed and the temperature was brought to -10 °C by means of a ice/salt bath. After 3 h at -10 °C, only trace **36** remained by TLC. Next add 35 ml of deionized water to the reaction mixture at -10 °C and stirred for 5 min. Striped off most of the THF and added to separatory funnel and extracted with ether until all of the organic was removed from the water phase. The combined ether phases were washed with saturated NaCl and then dried over sodium sulfate. The only products by TLC and NMR were the two BOC protected isomers of **37 and 38.** The isomers were separated by silica gel chromatography using 85% hexane and 15 % ethyl acetate; **BOC-37** (0.71 g) and **BOC- 38** (0.78 g).

Next the BOC protecting group was removed by reacting 0.87 g of **BOC-38** (1.78 mmoles) with 8.7 ml of 4 M HCl (34.8 mmoles)in dioxane for 30 min. Next added 4.74 g of sodium acetate (34.8 mmoles) to the reaction mixture and 16.5 ml ether and stirred until clear. After transferring to a separatory funnel extracted with ether and water and then dried the ether layer with sodium sulfate. After removing the ether, 0.665 g of **38** was isolated. Isomer **37** could be obtained in a similar procedure.

Example 23

(3α,4α,5α) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (40) and (3α,4β,5β) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (41)

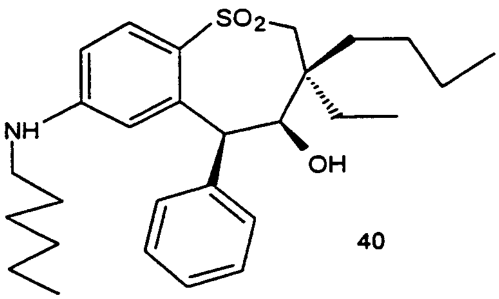
Step 1. 2-((2-Benzyl-4-(n-hexylamino)phenylsulfonyl)methyl)-2-ethylhexanal (39)



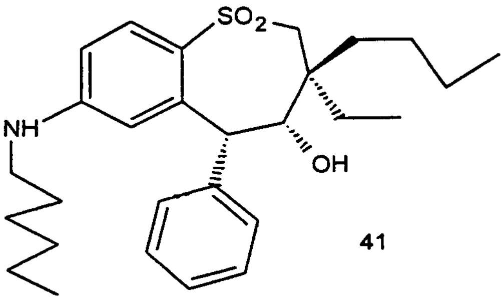
39

In a Fischer porter bottle weighed out 0.5 g of **34** (1.2 mmoles) and dissolved in 3.8 ml of ethanol under nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexanal. Seal and pressure to 50 psi of hydrogen gas. Stirred for 48 h. After filtering off the catalyst and removing the solvent by rotary evaporation **39** was isolated by column chromatography (0.16 g) using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. The product was characterized by NMR and mass spectra.

Step 2. (3α,4α,5α) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (40) and (3α,4β,5β) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (41)



40



41

A 2-neck, 25 ml round bottomed flask with stir bar was charged with 0.158 g **39** (0.335 mmole) and 5 ml anhydrous THF under nitrogen. Cool to -10 °C by means of a salt/water bath. Slowly add 0.113 g of potassium tert butoxide (0.335 mmole). After 15 min at -10 °C all of the starting material was consumed by TLC and only the two isomers **40** and **41** were observed. Next added 5 ml of chilled 10% HCl and stirred at -10 °C for 5 min. Transferred to a separatory funnel and extract with ether. Dried over sodium sulfate. Proton NMR of the dried product (0.143 g) indicated only the presence of the two isomers **40** and **41**. The two isomers were separated by silica gel chromatography using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. **40** (53.2 mg); **41**(58.9 mg).

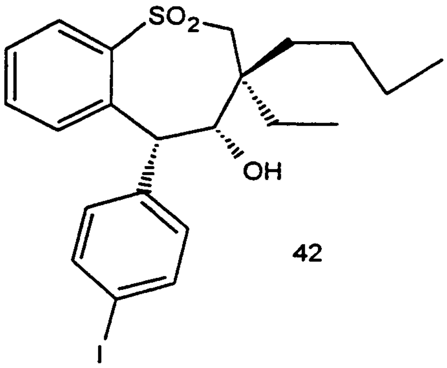
Example 24

Quaternization of amine substrates 40 and 41

Amine products such as **40** and **41** can be readily alkylated to quaternary salts by reaction with alkyl halides. For example **40** in DMF with 5 equivalents of methyl iodide in the presence of 2,6 dimethyl lutidine produces the dimethylhexylamino quaternary salt.

Example 25

(3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (42)

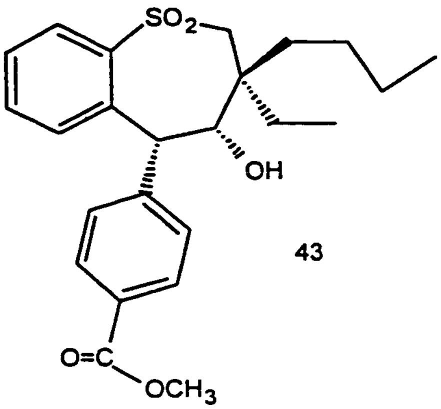


42

In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of **6d** , 0.67 g of mercuric triflate were dissolved in 20 ml of dry methylene chloride with stirring. Next 0.34 g of Iodine was added and the solution was stirred at room temperature for 30 h. The reaction was then diluted with 50 ml methylene chloride and washed with 10 ml of 1 M sodium thiosulfate; 10 ml of saturated KI ; and dried over sodium sulfate. See Tetrahedron, Vol.50, No. 17, pp 5139-5146 (1994) Bachki, F. Et al.Mass spectrum indicated a mixture of **6d** , mono iodide **42** and a diiodide adduct. The mixture was separated by column chromatography and **42** was characterized bt NMR and mass spectra.

Example 26

(3α,4β,5β) 3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (43)



43

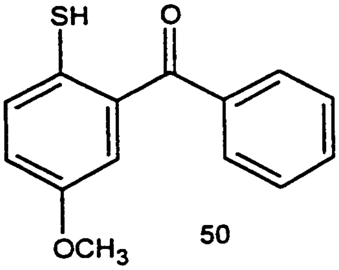
A 0.1 g sample of **42** (0.212 mmole), 2.5 ml dry methanol, 38 µl triethylamine (0.275 mmole) , 0.3 ml toluene and 37 mg of palladium chloride (0.21 mmole) was charged to a glass lined mini reactor at 300 psi carbon monoxide. The reaction was heated at 100 °C overnight. The catalyst was filtered and a high yield of product was isolated.
The product was characterized by NMR and mass spectra.

Note the ester functionalized product **43** can be converted to the free acid by hydrolysis.

Example 27

(3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)

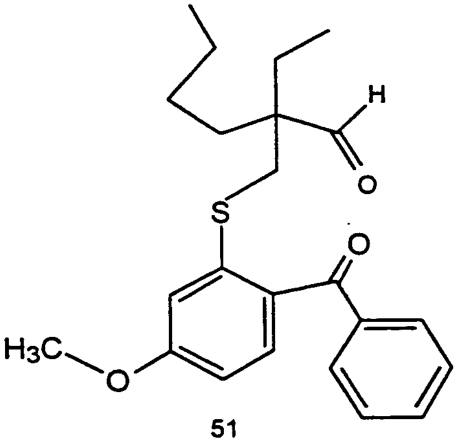
Step 1. 2-Mercapto-5-methoxybenzophenone (50)



50

Reaction of 66.2 g of 4-methoxythiophenol with 360 ml of 2.5 N n-butyllithium, 105 g of tetramethylethylenediamine and 66.7 g of benzonitrile in 600 ml cyclohexane according to the procedure in WO 93/16055 gave 73.2 g of brown oil which was kugelrohr distilled to remove 4-methoxythiophenol and gave 43.86 g of crude **50** in the pot residue.

Step 2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (51)

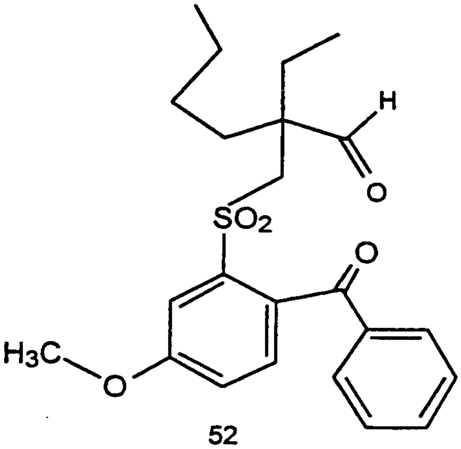


51

Reaction of 10 g (0.04 mole) of crude **50** with 4.8 g (0.02 mole)of mesylate **1** and 3.2 ml (0.23 mole) of triethylamine in 50 ml of diglyme according to the procedure for the preparation of **2** gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-hexane) to give 1.7 g (22%) of **51**.

Step 3. 2-((2-Benzoyl-4-methoxyphenylsulfonyl)methyl)-

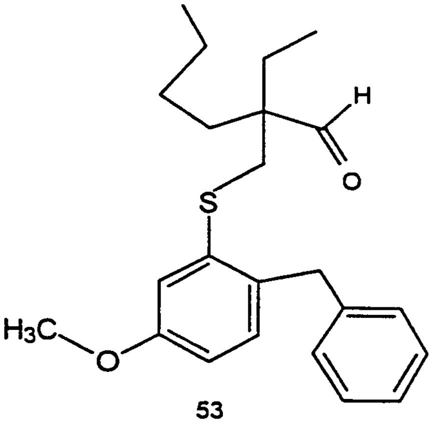
2-ethyl-hexanal (52)



52

A solution of 1.2 g (3.1 mmoles) of **51** in 25 ml of methylene chloride was reacted with 2.0 g (6.2 mmoles) of 50-60% MCPBA according to the procedure of step 2 of procedure A in example 18 gave 1.16 g (90%) of **52** as a yellow oil.

Step 4. 2-((2-Benzyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (53)

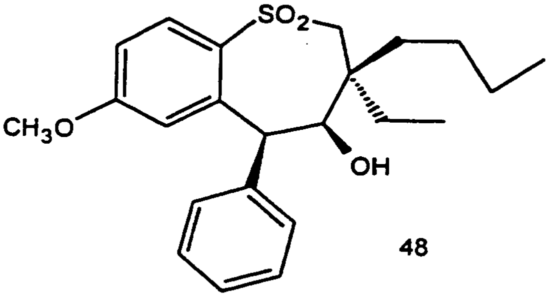


53

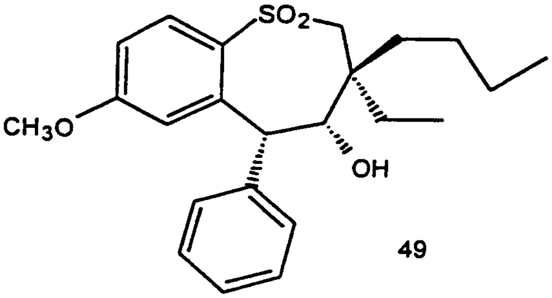
Hydrogenation of 1.1 g of **52** according to the procedure of step 3 of procedure A of example 18 gave **53** as a yellow oil (1.1 g).

Step 5. (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide

(48), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)



48



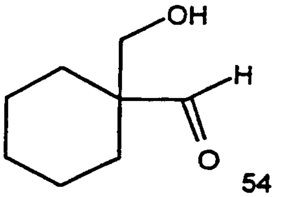
49

A solution of 1.1 g of **53**, 0.36 g of potassium t-butoxide and 25 ml of anhydrous THF was held at reflux for 2 h and worked up as in step 4 of procedure A of example 18 to give 1.07 g of a crude product which was purified by HPLC to give 40 mg (4%) of **48** as crystals, mp 153-154 °C and 90 mg (8%) of **49** as solid, mp 136-140 °C.

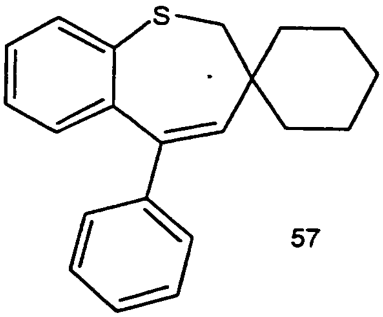
Example 28

5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)

Step 1. 1-(Hydroxymethyl)-cyclohexanecarboxaldehyde (54)



54

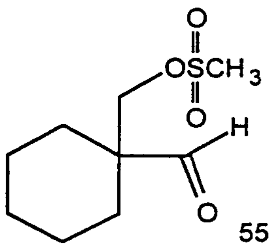


57

To a cold (0 °C) mixture of 100 g (0.891 mole) of cyclohexanecarboxaldehyde, 76.5 g of 37% of formaldehyde in 225 ml of methanol was added dropwise

90 ml of 1 N Sodium hydroxide in 1 h. The reaction mixture was stirred at room temperature over 48 then was evaporated to remove methanol. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 75 g (59.7%) of thick oil. Proton NMR and mass spectra were consistent with the product.

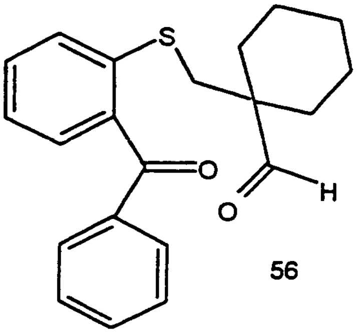
Step 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde (55)



55

To a cold (0 °C) mixture of alcohol **54** (75 g, 0.54 mole) and 65.29 g (0.57 mole) of methanesulfonyl chloride in 80 ml of methylene chloride was added a solution of pyridine (47.96 g, 0.57 mole) in 40 ml of methylene chloride. The reaction mixture was stirred at room temperature for 18 h then quenched with water, acidified with conc. HCl and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 91.63 g (77.8%) of thick oil. Proton NMR and mass spectra were consistent with the product.

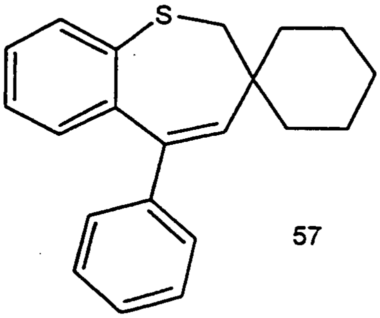
Step 3. 1-((2-Benzoylphenylthio)methyl)cyclohexanecarboxaldehyde (56)



56

A mixture of 69 g (0.303 mole) of 2-mercaptobenzophenone, 82 g (0.303 mole) of mesylate **55**, 32 g of triethylamine, and 150 ml of diglyme was stirred and held at reflux for 24 h. The mixture was cooled, poured into dil. HCl and extracted with methylene chloride. The organic layer was washed with 10% NaOH, water, brine, and dried over sodium sulfate and concentrated under vacuum to remove excess diglyme. This was purified by silica gel flush column (5% EtOAc: Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton NMR and mass spectra were consistent with the product.

Step 4. 5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)

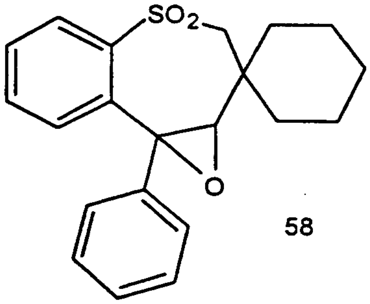


57

To a mixture of 6.19 g of zinc dust and 100 ml of dry DME was added $TiCl_3$(16.8 g, 0.108 mole) . The reaction mixture was heated to reflux for 2 h. A solution of compound **56** (8.3 g, 0.023 mole) in 50 ml of DME was added dropwise to the reaction mixture in 1 h and the mixture was held at reflux for 18 h. The mixture was cooled, poured into water and extracted with ether. The organic layer was washed with water, brine, and dried over sodium sulfate, filtered through celite and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white solid, mp 90-91 °C. Proton and carbon NMR and mass spectra were consistent with the product.

Example 29

8b-Phenyl-1a,2,3,8b-tetrahydrospiro(benzothiepino[4,5-b]oxirene-2,1′-cyclohexane)-4,4-dioxide (58)

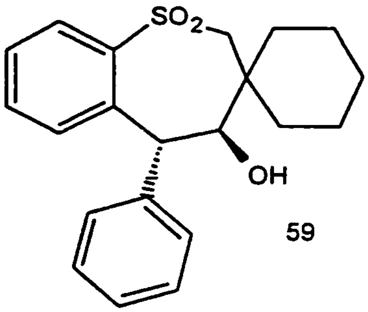


58

To a solution of **57** (4.6 g, 15 mmole) in 50 ml chloroform under nitrogen was added 55% MCPBA (16.5 g, 52.6 mmole) portionwise with spatula. The reaction was held at reflux for 18 h and washed with 10% NaOH(3X), water, brine, and dried over sodium sulfate and concentrated under vacuum to give 5 g of crude product. This was recrystallized from Hexane/EtOAc to give 4.31 g (81%) of yellow solid, mp 154-155 °C. Proton and carbon NMR and mass spectra were consistent with the product.

Example 30

trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1′-cyclohexane)-1,1-dioxide (59)

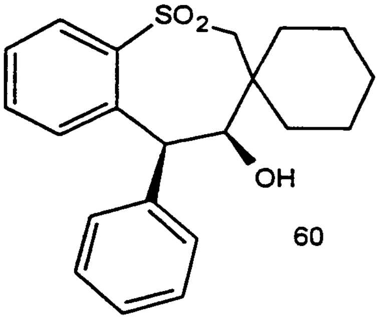


59

A mixture of 0.5 g (1.4 mmoles) of **58** , 20 ml of ethanol,10 ml of methylene chloride and 0.4 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to dryness. The residue was purified by HPLC (10% EtOAc-Hexane, 25% EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was a trans isomer. The second fraction gave 200 mg of solid which was impure cis isomer.

Example 31

cis-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (60)



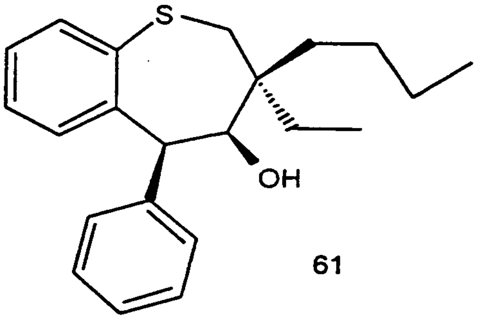
60

To a solution of 0.2 g (0.56 mmole) of **59** in 20 ml of CH_2Cl_2, was added 8 g of 50% NaOH and one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst. The reaction mixture was stirred for 10 h at room temperature. Twenty g of ice was added to the mixture and the mixture was extracted with CH_2Cl_2

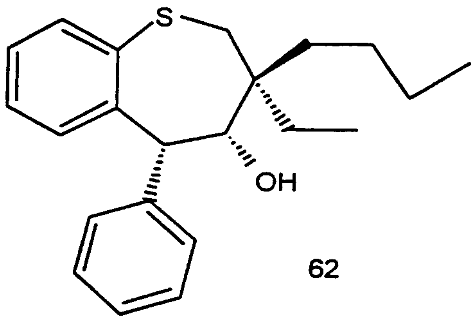
(3x10 ml) washed with water, brine and dried over $MgSO_4$ and concentrated in vacuo to recover 0.15 g of crude product. This was recrystallized from Hexane/EtOAc to give 125 mg of white crystal, mp 209-210 °C . Proton and carbon NMR and mass spectra were consistent with the product.

Example 32

(3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (61), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (62)



61



62

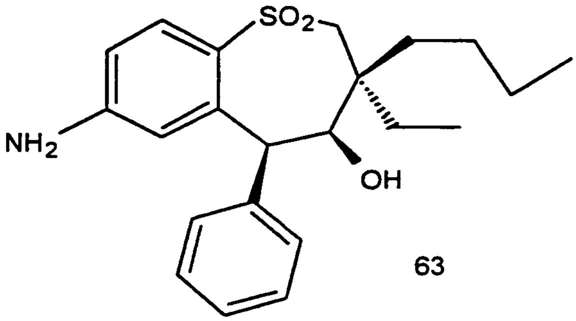
To a solution of 0.5 g (1.47 mmole) of compound **47** in 5 ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred at room temperature for 18 h and quenched with 10 ml of 10% HCl. The organic was extracted into methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by HPLC (2% EtOAc-hexane) to give 47 mg of **61** in the second fraction and 38 mg of **62** in the third fraction. Proton NMR and mass spectra were consistent with the assigned structures.

Example 33

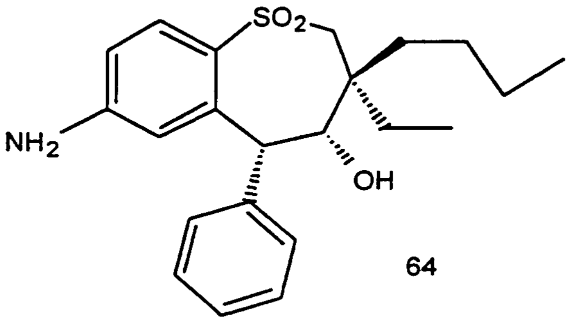
(3α,4α,5α) 3-Butyl-3ethyl-4-hydroxy-7-amino-5-phenyl-

10068297.020802

2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (63) and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide(64)



63

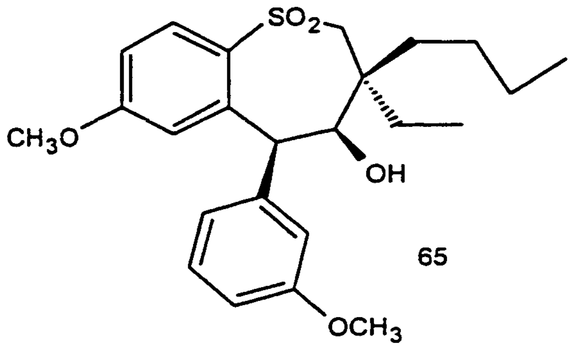


64

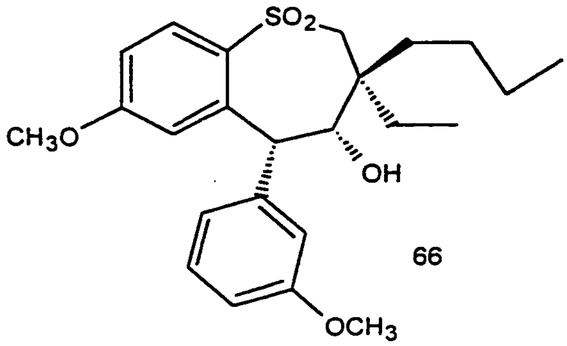
An autoclave was charged with 200 mg of **37** in 40 cc ethanol and .02 g 10 % Pd/C. After purging with nitrogen the clave was charged with 100 psi hydrogen and heated to 55 C. The reaction was monitored by TLC and mass spec and allowed to proceed until all of **37** was consumed. After the reaction was complete the catalyst was filtered and the solvent was removed in vacuo and the only observable product was amine **63**. This same procedure was used to produce **64** from **38**.

Example 34

(3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (65), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (66).



65

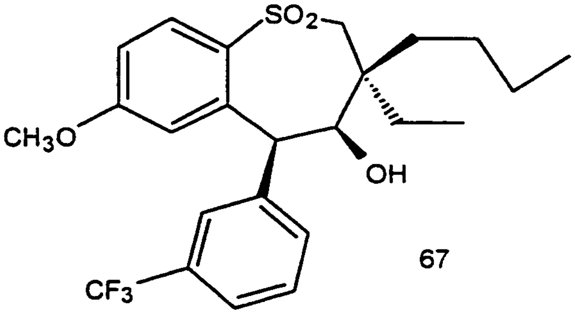


66

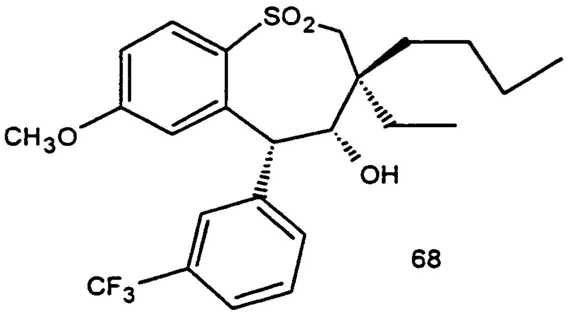
Alkylation of e-methoxyphenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-methoxybenzyl)phenol in 35% yield. This material was converted to compound 65, mp 138.5-141.5 °C, and compound 66, mp 115.5-117.5 °C, by the procedure similar to that in Example 18 method B.

Example 35

(3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (67), and (3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (68).



67

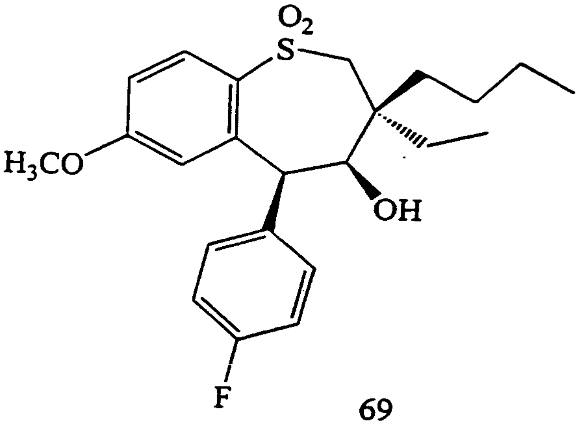


68

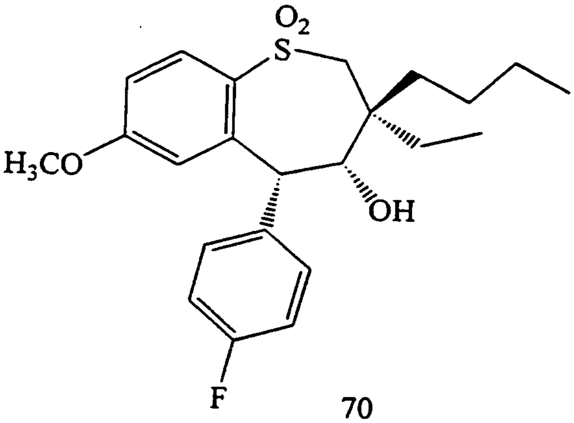
Alkylation of 4-methoxyphenol with 3-(trifluoromethyl)benzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-(trifluoromethyl)benzyl)phenol. This material was converted to compound 67, mp 226.5-228 °C, and compound 68, mp 188-190°C, byu the procedure similar to that in Example 18 method B.

Example 36

(3α,4α,5α) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (69), and (3α,4β,5β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (70).



69



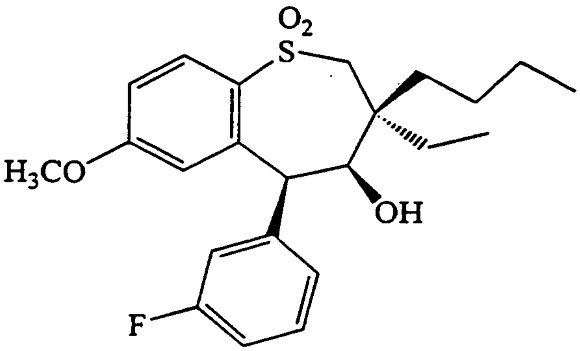
70

Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(4'-fluorobenzyl)phenol. This material was converted to compound 69 and compound 70 by the procedure similar to that in Example 18 method B.

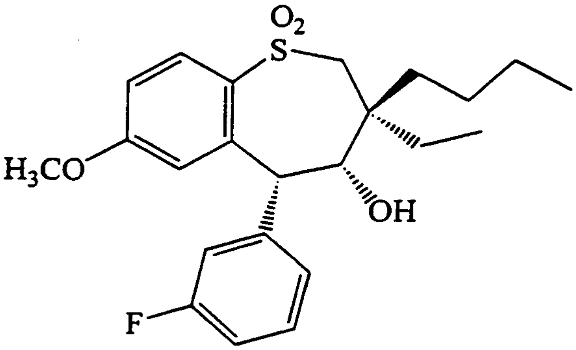
Example 37

(3α,4α,5α) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (71), and (3α,4β,5β) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-

tetrahydrobenzothiepine-1,1-dioxide (72).



71

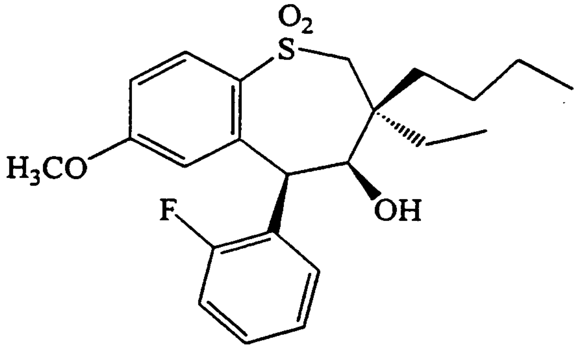


72

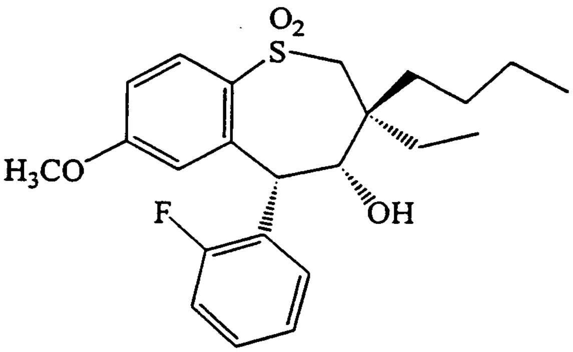
Alkylation of 4-methoxyphenol with 3-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-fluorobenzyl)phenol. This material was converted to compound 71 and compound 72 by the procedure similar to that in Example 18 method B.

Example 38

(3α,4α,5α) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and (3α,4β,5β) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).



73



74

Alkylation of 4-methoxyphenol with 2-fluorobenzyl

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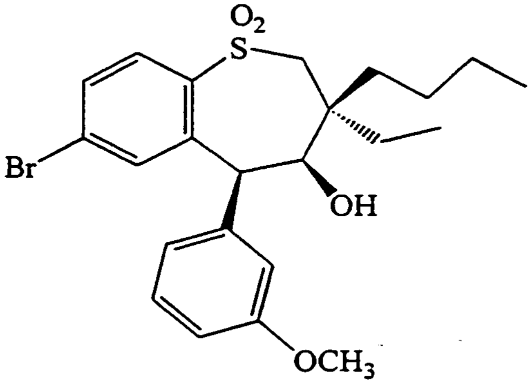
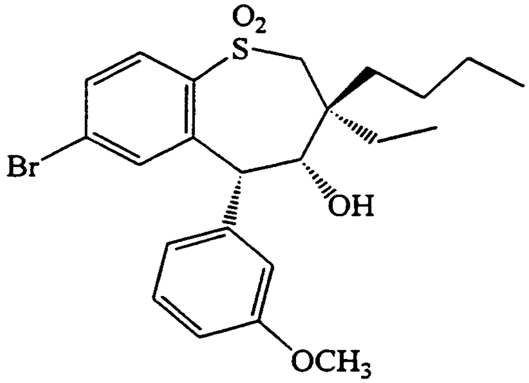
chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

Example 39

(3α,4α,5α) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (75), and (3α,4β,5β) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).



75



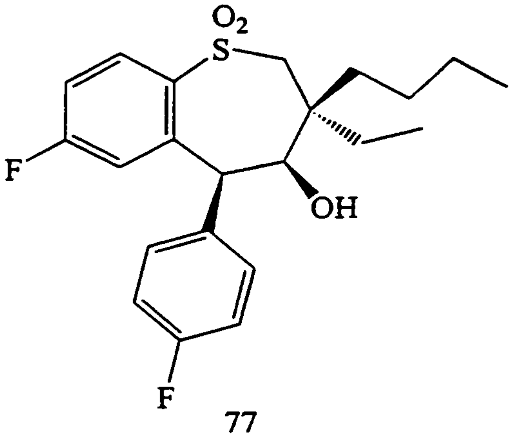
76

Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.

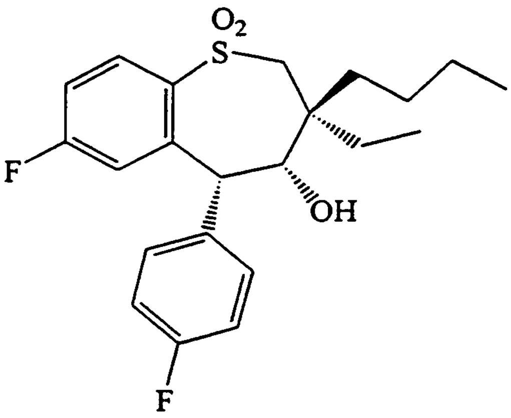
Example 40

(3α,4α,5α) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (77), and

(3α,4β,5β) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (78).



77

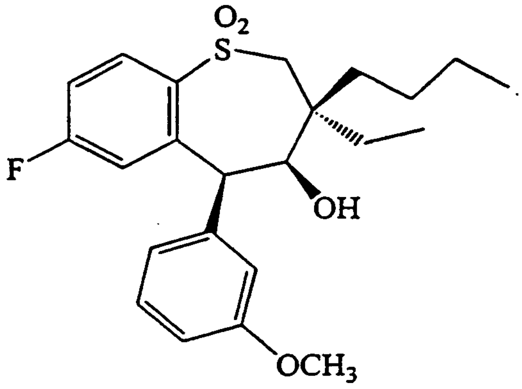


78

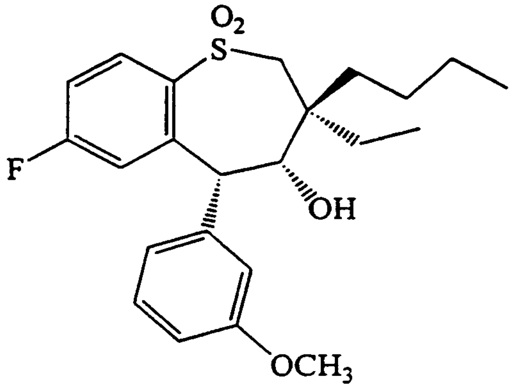
Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230 °C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

Example 41

(3α,4α,5α) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and (3α,4β,5β) 3-Butyl-3-ethyl-7-fluoro-40hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (80).



79

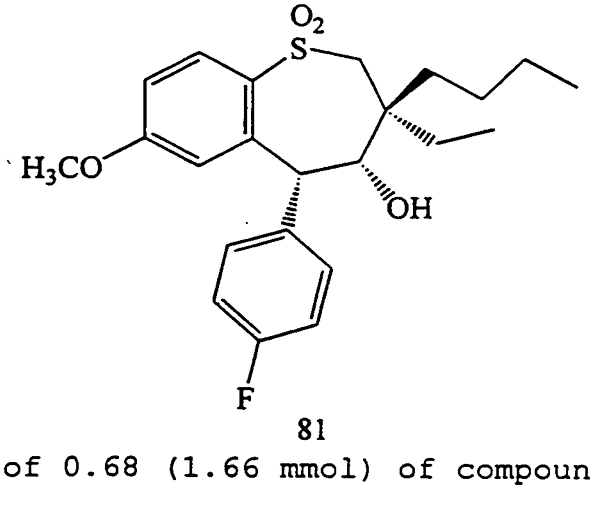


80

Alkylation of 4-fluorophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-methoxybenzyl)phenol. This material was converted to compound 79, as a solid and compound 80, mp 153-155 °C, by the procedure similar to that in Example 18 method B.

Example 42

(3α,4β,5β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (81).

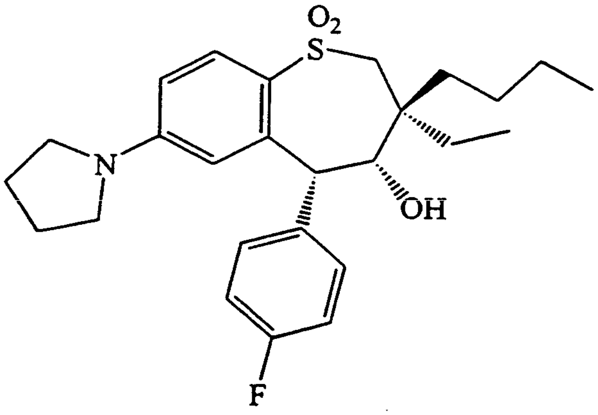


81

A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was dilute with ether and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20% ethyl acetate in hexanes). The first fraction was impure (3α,4α,5α) 3-butyl-3-ethyl-4-hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide. The second fraction was compound 81, mp 185-186.5 °C.

Example 43

(3α,4β,5β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-pyrrolidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (82).

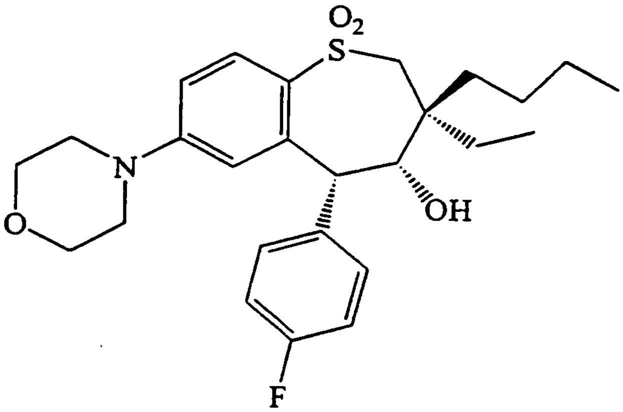


82

A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml of pyrrolidine was held at reflux for 1 h. The reaction mixture was diluted with ether and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was crystallized from ether-hexanes to give compound 82, mp 174.5-177 °C.

Example 44

(3α,4β,5β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-morpholinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (83).

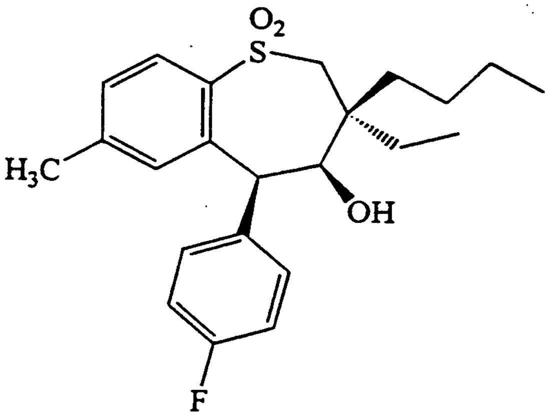


83

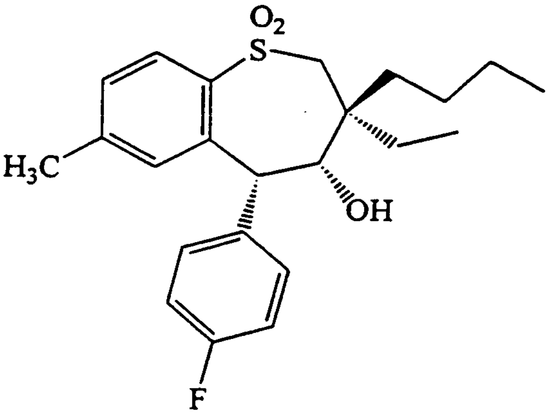
A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g (56 mmol) of morpholine was held at reflux for 2 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was recrystallized from ether-hexanes to give compound 83, mp 176.5-187.5 °C.

Example 45

(3α,4α,5α) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (84), and (3α,4β,5β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (85).



84

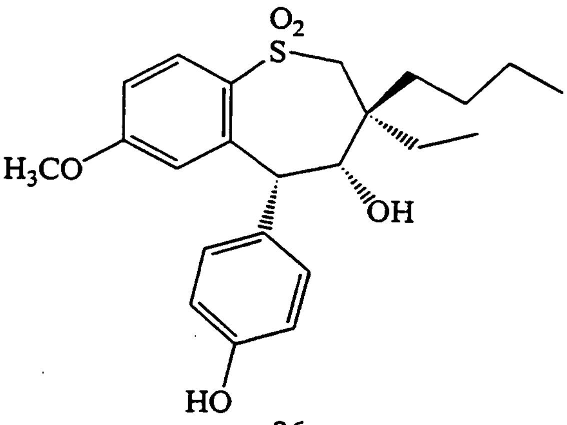


85

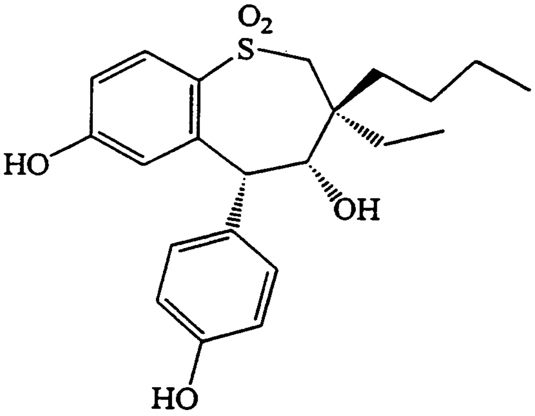
Alkylation of 4-methylphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methyl-2-(4'-fluorobenzyl)phenol). This material was converted to compound 84 and compound 85 by the procedure similar to that in Example 18 method B.

Example 46

(3α,4β,5β) 3-Butyl-3-ethyl-4-hydroxy-5-(4'-hydroxyphenyl)-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (86), and (3α,4β,5β) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (87).



86

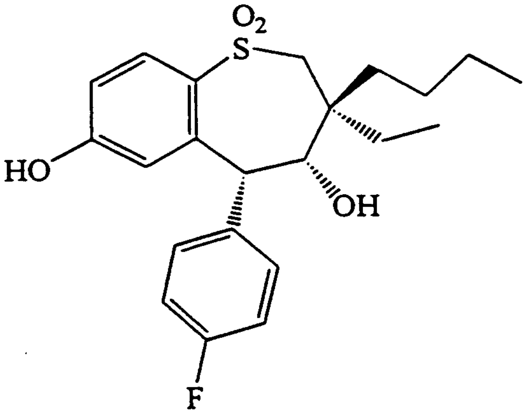


87

To a solution of 0.52 (1.2 mmol) of compound 66 in 20 ml of methylene chloride was added 1.7 g (6.78 mmol) of born tribromide. The reaction mixture was cooled to -78 °C and was stirred for 4 min. An additional 0.3 ml of boron tribromide was added to the reaction mixture and the reaction mixture was stirred at -78 °C for 1 h and quenced with 2 N HCl. The organic was extracted into ether. The ether layer was washed with brine, dried over M_gSO_4, and concentrated in vacuo. The residue (0.48 g) was purified by HPLC (30% ethyl acetate in hexanes). The first fraction was 0.11 g of compound 86 as a white solid, mp 171.5-173 °C. The second fraction was crystallized from chloroform to give 0.04 g of compound 87 as a white solid, mp 264 °C (dec).

Example 47

(3α,4β,5β) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (88).

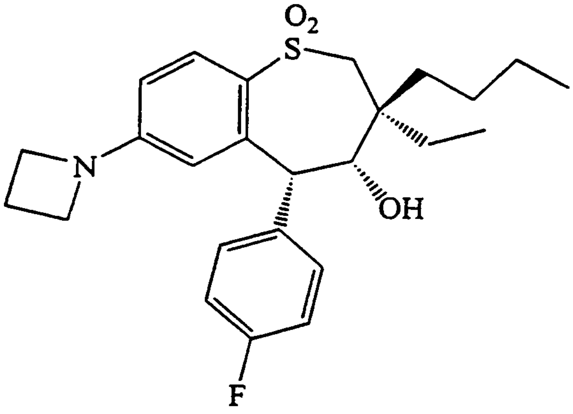


88

Reaction of compound 70 with excess boron tribromide at room temperature and worked up as in Example 46 gave compound 88 after an HPLC purification.

Example 48

(3α,4β,5β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-azetidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (89).

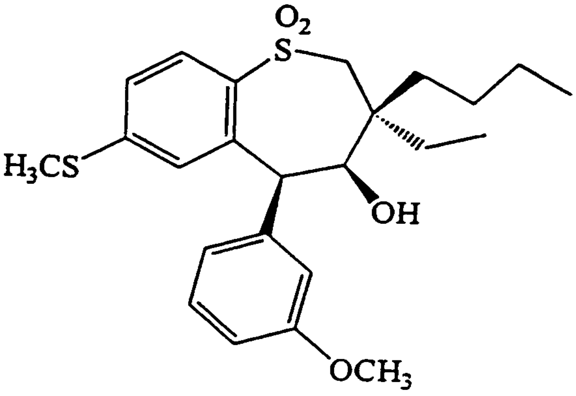


89

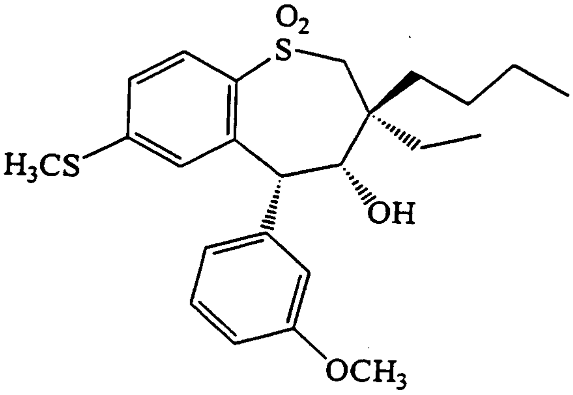
A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 g (35 mmol) of aztidine was held at reflux for 3 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over MgSO4. The ether solution was concentrated on a steam bath. The separated crystals were filtered to give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.

Example 49

(3α,4α,5α) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (90). (3α,4β,5β) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (91).



90

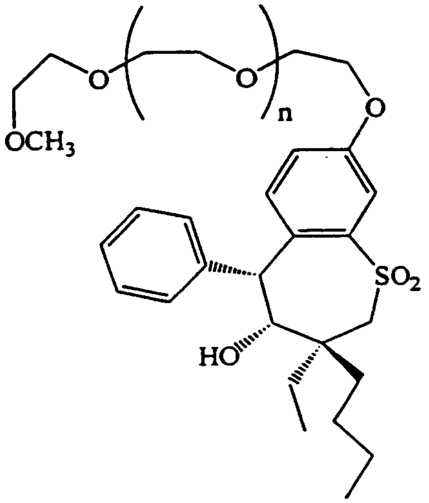


91

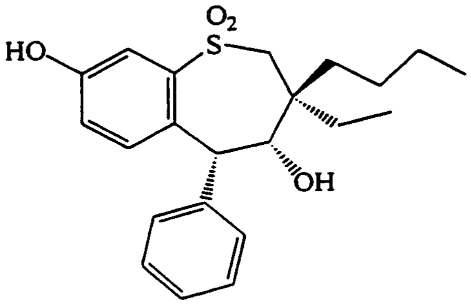
A mixture of 0.4 g (0.95 mmol) of compound 79, 0.08 g (1.14 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at 60 °C for 2 h. An additional 1.4 mmol of sodium methanethiolate was added to the reaction mixture and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was triturated with 100 ml of water and extracted methylene chloride. The methylene chloride water mixture was filtered through Celite and the methylene chloride layer was dried over M_gSO_4 and concentrated in vacuo. The first fraction (0.1 g) was compound 90, mp 117-121 °C. The second fraction (0.16 g) was compound 91, mp 68-76 °C.

Example 50

Preparation of polyethyleneglycol functionalized benzothiepine A.



No. 141



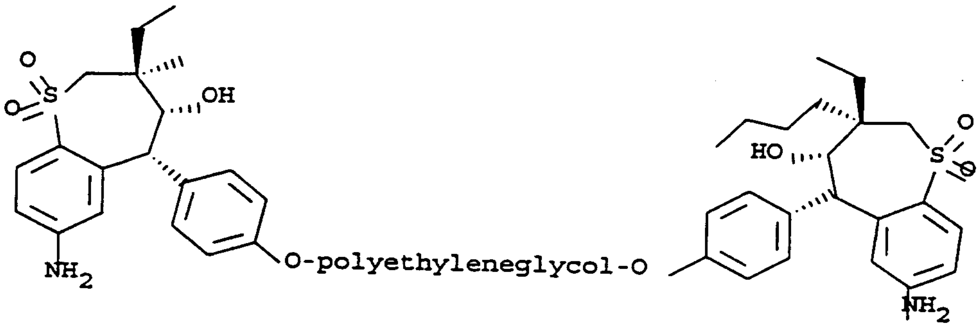
No. 136

A 50 ml rb flash under a nitrogen atmosphere was charged with 0.54 g of M-Tres-5000 (Polyethyleneglycol Tresylate [methoxy-PEG-Tres,MW 5000] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.055 g Compound No. 136, 0.326 C_sCO_3 and 2cc anhydrous acetonitrile. The reaction was stirred at 30 C for 5 days and then the solution was filtered to remove salts. Next, the acetonitrile was removed under vacuum and the product was dissolved in THF and then precipitated by addition of hexane. The polymer precipitate was isolate by filtration from the solvent mixture (THF/hexane). This precipitation procedure was continued until no Compound No. 136 was detected in the precipitated product (by TLC SiO2). Next, the polymer precipitate was dissolved in water and filtered and the water soluble polymer was dialyzed for 48 hours through a cellulose dialysis tube (Spectrum® 7 ,45 mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried. The NMR was consistent with the desired product A and gel permeation chromatography indicated the presence of a 4500 MW polymer and also verified that no free Compound

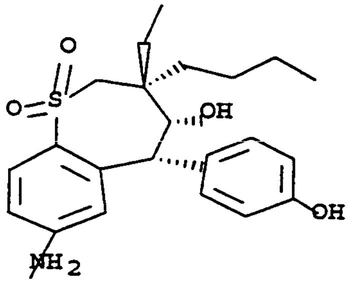
No. 136 was present. This material was active in the IBAT in vitro cell assay.

Example 51

Preparation of Compound 140



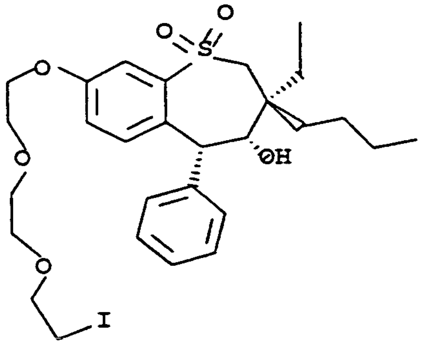
No. 140



No. 111

A 2-necked 50 ml round bottom Flask was charged with 0.42g of Tres-3400 (Polyethyleneglycol Tresylate [Tres-PEG-Tres,MW 3400] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.1 potassium carbonate, 0.100g of Compound No. 111 and 5 ml anhydrous DMF. Stir for 6 days at 27 °C. TLC indicated the disappearance of the starting Compound No. 111. The solution was transferred to a separatory funnel and diluted with 50 cc methylene chloride and then extracted with water. The organic layer was evaporated to dryness by means of a rotary evaporator. Dry wgt. 0.4875 g. Next, the polymer was dissolved in water and then dialyzed for 48 hours at 40 °C through a cellulose dialysis tube (spectrum® 7 ,45mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried 0.341 g). NMR was consistent with the desired product B.

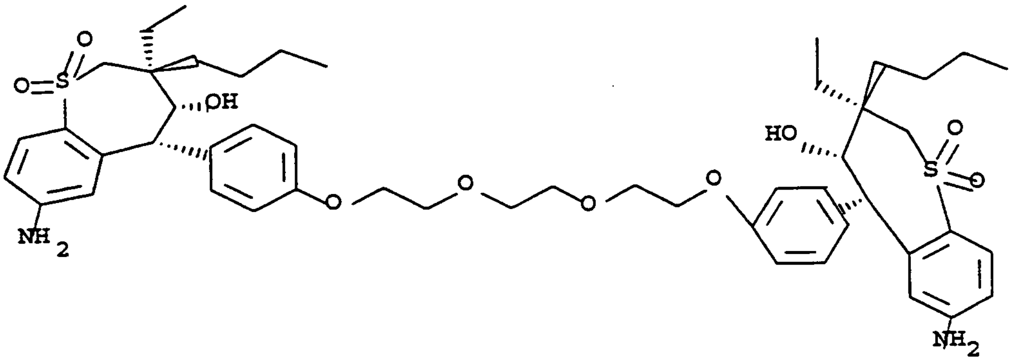
Example 52



No. 134

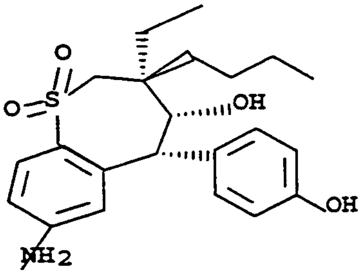
A 10 cc vial was charged with 0.21 g of Compound No. 136 (0.5mmoles), 0.17g (1.3 mmoles)potassium carbonate, 0.6g (1.5 mmoles) of 1,2-bis-(2-iodoethoxy)-ethane and 10 cc DMF. The reaction was stirred for 4 days at room temperature and then worked up by washing with ether/water. The ether layer was stripped to dryness and the desired product Compound No. 134 was isolated on a silica gel column using 80/20 hexane ethyl acetate.

Example 53


O
O
S
OH
NH2
O
O
O
O
HO
O
S
O
NH2

No. 112

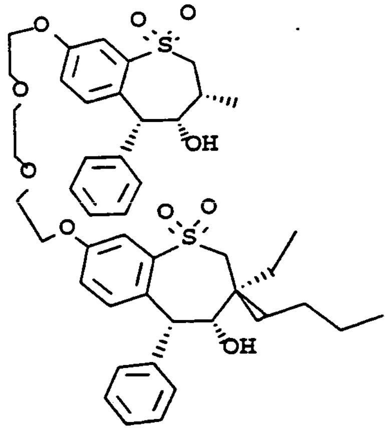
Example 54


O
O
S
OH
OH
NH2

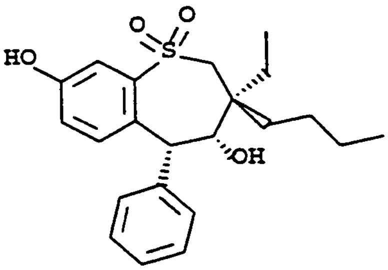
No. 113

A two necked 25 ml round bottom Flask was charged with 0.5g (1.24mmoles) of 69462, 13 mls of anhydrous DMF, 0.055g of 60% NaH dispersion and 0.230g (0.62 mmoles) of 1,2-Bis [2-iodoethoxylethane] at 10 °C under nitogen. Next, the reaction was slowly heated to 40 °C. After 14 hours all of the Compound No. 113 was consumed and the reaction was cooled to room temperature and extracted with ether/water. The ether layer was evaporated to dryness and then chromatographed on Silicage (80/20 ethyl acetate/hexane). Isolated Compound No. 112 (0.28 g) was characterized by NMR and mass spec.

Example 55



No. 135



No. 136

In a 50 ml round bottom Flask, add 0.7g (1.8 mmoles) of Compound No. 136, 0.621g of potassium carbonate, 6 ml DMF, and 0.33g of 1,2-Bis [2-iodoethoxylethane]. Stir at 40 °C under nitrogen for 12 hours. The workup and isolation was the same procedure for Compound No. 112.

Examples 56 and 57 (Compound Nos. 131 and 137)

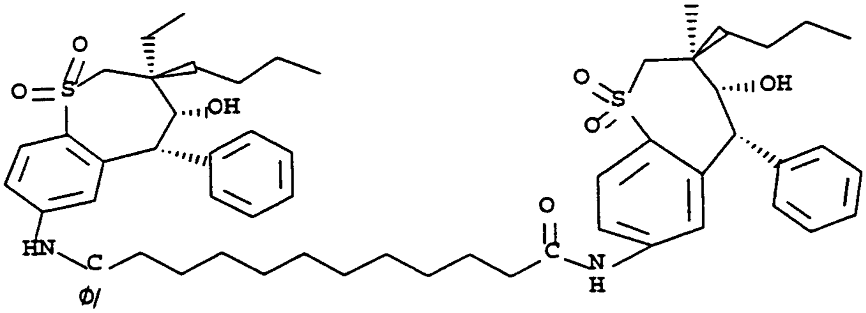
The compositions of these compounds are shown in Table 3.

The same procedure as for Example 55 except appropriate benzothiepine was used.

Example 58 (Compound No. 139)

The composition of this compound is shown in Table 3. Same procedure as for Example 55 with appropriate benzothiepine 1,6 diiodohexane was used instead of 1,2-Bis [2-iodoethoxylethane].

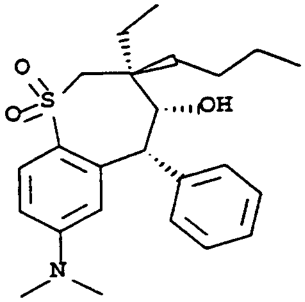
Example 59 (Compound No. 101)



No. 101

This compound is prepared by condensing the 7-NH_2 benzothiepine with the 1,12-dodecane dicarboxylic acid or acid halide.

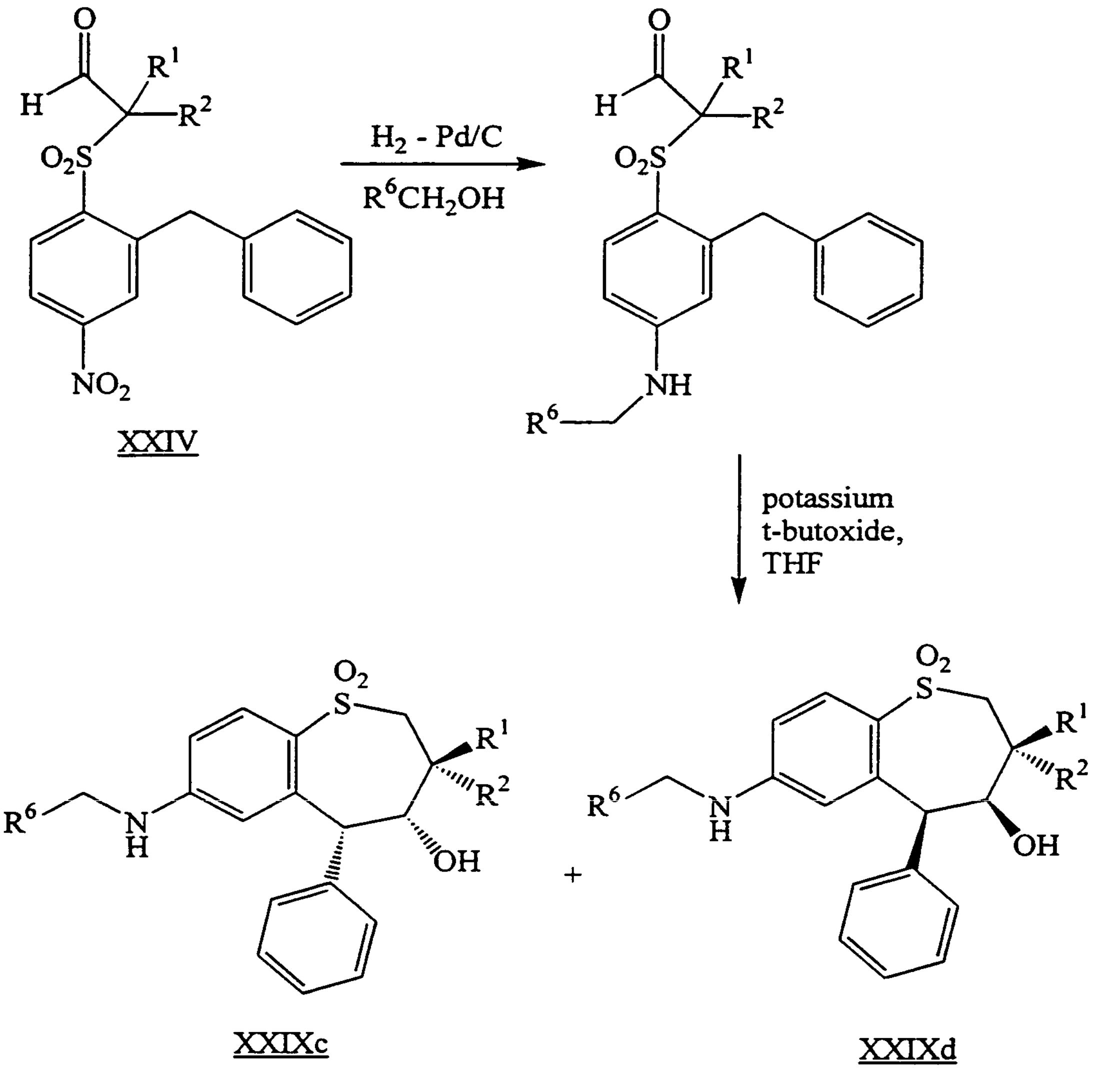
Example 60 (Compound No. 104)



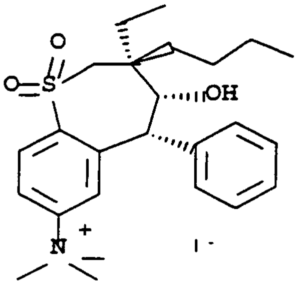
No. 104

2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 5). Reduction of the sulfone-aldehyde XXV formaldehyde and 100 psi hydrogen and 55 C for 12 hours catalyzed by palladium on carbon in the same reaction vessel yields the substituted dimethylamine derivative XXVIII. Cyclization of XXVII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention Compound No. 104.

Scheme 6


H
O
R^1
R^2
O_2S
NO_2
XXIV
H_2 - Pd/C
R^6CH_2OH
NH
R^6
potassium
t-butoxide,
THF
O_2
S
OH
N
H
+
XXIXc
XXIXd

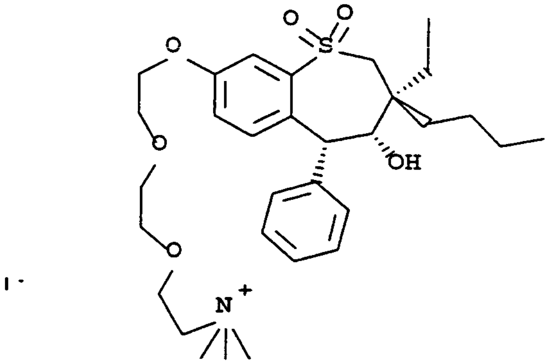
Example 61



No. 102

A 1 oz. Fisher-porter bottle was charged with 0.14 g (0.34 mmoles) of 70112, 0.97 gms (6.8 mmoles) of methyl iodide, and 7 ml of anhydrous acetonitrile. Heat to 50 °C for 4 days. The quat. Salt Compound No. 192 was isolated by concentrating to 1 cc acetonitrile and then precipitating with diethyl ether.

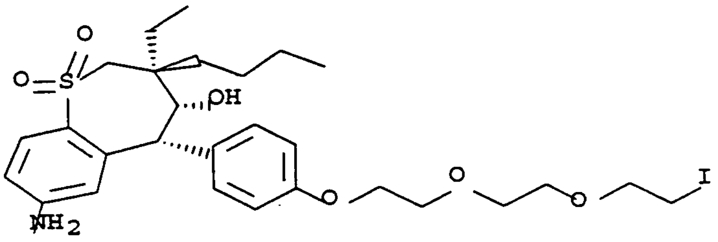
Example 62



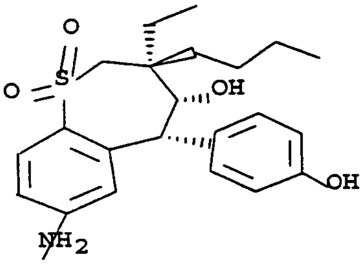
No. 125

A 0.1 g (0.159 mmoles) sample of Compound No. 134 was dissolved in 15 ml of anhydrous acetonitrile in a Fischer-porter bottle and then trimethylamine was bubbled through the solution for 5 minutes at 0 °C and then capped and warmed to room temperature. The reaction was stirred overnight and the desired product was isolated by removing solvent by rotary evaporation.

Example 63 (Compound No. 295)



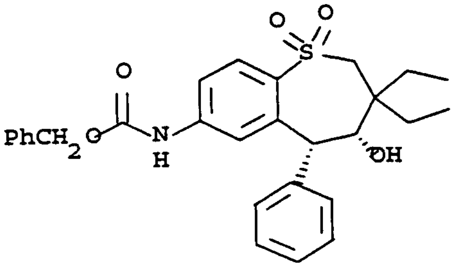
No. 295



No. 113

Sodium Hydride 60% (11 mg, 0.27 mmoles) in 1 cc of acetonitrile at 0 °C was reacted with 0.248 mmoles (.10 g) of Compound No. 54 in 2.5cc of acetonitrile at 0 °C. Next, 0.(980g 2.48 mmoles) of 1,2-Bis [2-iodoethoxylethane]. After warming to room temperature, stir for 14 hours. The product was isolated by column chromatography.

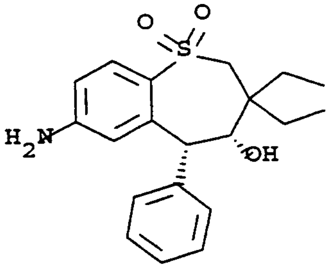
Example 64 (Compound No. 286)



No. 286

Following a procedure similar to the one described in Example 86, infra (see Compound No. 118), the title compound was prepared and purified as a colorless solid; mp 180-181 °C; ^{1}H NMR ($CHCl_3$) δ 0.85 (t, J = 6 Hz, 3H_, 0.92 (t, J = 6 Hz, 3H), 1.24-1.42 (m, 2H), 1.46-1.56 (m, 1H), 1.64-1.80 (m, 1H), 2.24-2.38 (m, 1H), 3.15 (AB, J_{AB} = 15 Hz, Δv = 42 Hz, 2H), 4.20 (d, J = 8 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.46 (s, 1H), 6.68 (s, 1H), 7.29-7.51 (m, 10H), 7.74 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H). FABMS m/z 494 (M+H), HRMS calcd for (M+H) 494.2001, found 494.1993. Anal. Calcd. for $C_{28}H_{31}NO_5S$: C, 68.13; H, 6.33; N, 2.84. Found: C, 68.19; H, 6.56; N, 2.74.

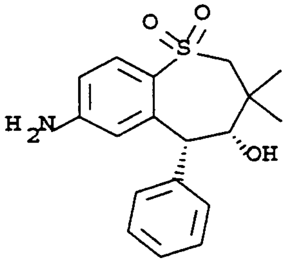
Example 65 (Compound No. 287)



No. 287

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless solid: mp 245-246 °C, ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6 Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.28, (d, J = 8 Hz, 1H), 1.32-1.42 (m, 1H), 1.48-1.60 (m, 1H), 1.64-1.80 (m, 1H), 2.20-2.36 (m, 1H), 3.09 (AB, J_{AB} = 15 Hz, Δv = 42 Hz, 2H), 3.97 (bs, 2H), 4.15 (d, J = 8 Hz, 1H), 5.49 (s, 1H), 5.95 (s, 1H), 6.54 (d, J = 7 Hz, 1H), 7.29-7.53 (m, 5H), 7.88 (d, J = 8 Hz, 1H); ESMS 366 (M+Li). Anal. Calcd. for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.54; H, 7.20; N, 3.69.

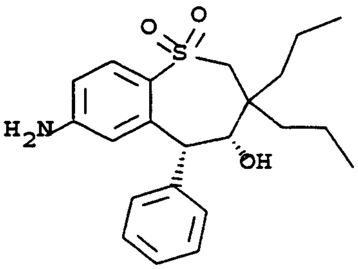
Example 66 (Compound No. 288)



No. 288

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified by silica gel chromatography to give the desired product as a colorless solid: mp 185-186°C; ^{1}H NMR ($CDCl_3$) δ1.12 (s, 3H), 1.49 (s, 3H), 3.00 (d, J = 15 Hz, 1H), 3.28 (d, J = 15 Hz, 1H), 4.00 (s, 1H), 5.30 (s, 1H), 5.51 (s, 1H), 5.97 (s, 1H), 6.56 (dd, J = 2.1, 8.4 Hz, 1H), 7.31-7.52 (m, 5H), 7.89 (d, J = 8.4 Hz, 1H). MS (FAB+) (M+H) m/z 332.

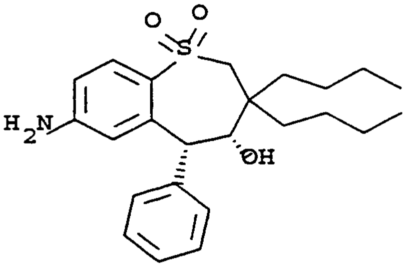
Example 67 (Compound No. 289)



No. 289

Following a procedure similar to the one described in Example 89 (see Compound No. 121), the title compound was prepared and purified by silica gel chromatography to give the desired product as a white solid: mp 205-206 °C; ^1H NMR ($CDCl_3$) δ 0.80-0.95 (m, 6H), 1.10-1.70 (m, 7H), 2.15 (m, 1H), 3.02 (d, J = 15.3 Hz, 2H), 3.15 (d, J = 15.1 Hz, 2H), 3.96 (s, br, 2H), 4.14 (d, J = 7.8 Hz, 1H), 5.51 (s, 1H), 5.94 (d, J = 2.2, 1H), 6.54 (dd, J = 8.5, 2.2 Hz, 1H), 7.28-7.50 (m, 6H), 7.87 (d, J = 8.5 Hz, 1H). MS (FAB): m/z 388 (M+H).

Example 68 (Compound No. 290)

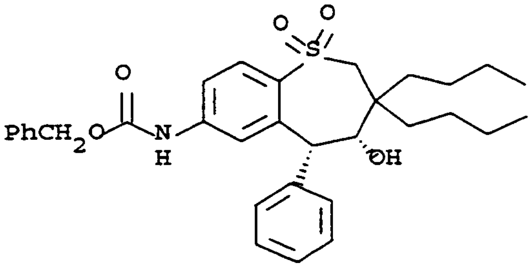


No. 290

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless solid: mp = 96-98 °C, ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7

Hz, 6H), 1.03-1.70 (m, 11H), 2.21 (t, J = 8 Hz, 1H), 3.09 (AB, J_{AB} =- 18 Hz, Δv = 38 Hz, 2H), 3.96 (bs, 2H), 4.14 (d, J = 7 Hz, 1H), 5.51 (s, 1H), 5.94 (s, 1H), 6.56 (d, J = 9 Hz, 1H), 7.41-7.53 (m, 6H), 7.87 (d, J = 8 Hz, 1H); FABMS m/z 416 (M+H).

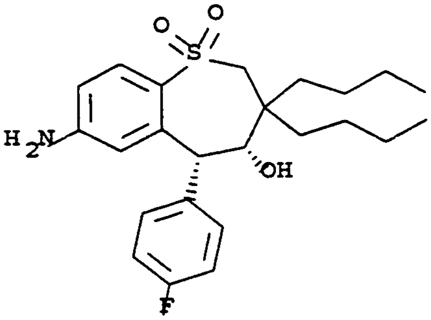
Example 69



No. 291

Following a procedure similar to the one described in Example 86, infra (see Compound No. 118), the title compound was prepared and purified as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 6H), 1.02-1.52 (m, 11H), 1.60-1.70 (m, 1H), 2.23 (t, J = 8 Hz, 1H), 3.12 (AB, J_{AB} = 18 Hz, Δv = 36 Hz, 2H), 4.18 (d, J = 7 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.43 (s, 1H), 6.65 (s, 1H), 7.29-7.52 (m, 10H), 7.74 (d, J = 9 Hz, 1H), 8.03 (d, J = 8 Hz, 1H); ESMS m/z 556 (M+Li).

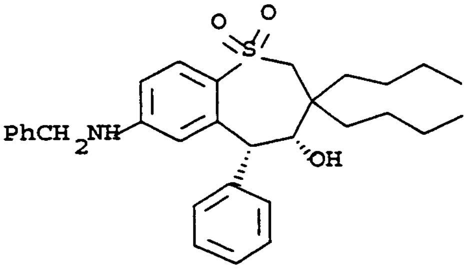
Example 70 (Compound No. 292)



No. 292

Following a procedure similar to the one descried in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless solid: mp = 111-112.5°C, ^{1}H NMR (CDCl$_3$) δ 0.90 (t, J = 8 Hz, 6H), 1.03-1.50 (m, 10H), 1.55-1.70 (m, 2H), 2.18 (t, J = 12 Hz, 2H), 3.07 (AB, J_{AB} = 15 Hz, Δv = 45 Hz, 2H), 4.09 (bs, 2H), 5.49 (s, 1H), 5.91 (s, 1H), 6.55 (d, J = 9 Hz, 1H), 7.10 (t, J = 7 Hz, 2H), 7.46 (t, J = 6 Hz, 2H), 7.87 (d, J = 9 Hz, 1H).

Example 71 (Compound No. 293)



No. 293

During the preparation of Compound No. 290 from Compound No. 291 using BBr$_3$, the title compound was isolated: ^{1}H NMR (CDCl$_3$) δ 0.85 (t, J = 6 Hz, 6H), 0.98-1.60 (m, 10H), 1.50-1.66 (m, 2H), 2.16 (t, J = 8 Hz, 1H), 3.04 (AB, J_{AB} = 15 Hz, Δv = 41 Hz, 2H), 4.08 (s, 1H), 4.12 (s, 1H), 5.44 (s, 1H), 5.84 (s, 1H), 6.42 (d, J = 9 Hz, 1H), 7.12 (d, J = 8 Hz, 2H), 7.16-7.26 (m, 10H), 7.83 (d, J = 8 Hz, 1H); ESMS m/z 512 (M+Li).

Example 72 (Compound No. 294)

Following a procedure similar to the one described in Example 60 (Compound No. 104), the title compound was prepared and purified as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6 Hz, 6H), 1.05-1.54 (m, 9H), 1.60-1.70 (m, 1H), 2.24 (t, J = 8 Hz, 1H), 2.80 (s, 6H), 3.05 (AB, J_{AB} = 15 Hz, Δv = 42 Hz, 2H), 4.05-4.18 (m, 2H), 5.53 (s, 1H), 5.93 (s, 1H), 6.94 (d, J = 9 Hz, 1H), 7.27-7.42 (m, 4H), 7.45 (d, J = 8 Hz, 2H), 7.87 (d, J = 9 Hz, 1H); ESMS m/z 444 (M+H).

Structures of the compounds of Examples 33 to 72 are shown in Tables 3 and 3A.

Examples 73-79, 87, 88 and 91-102

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, compounds were prepared having the structures set forth in Table 3. The starting materials illustrated in the reaction schemes shown above were varied in accordance with principles of organic synthesis well known to the art to introduce the indicated substituents in the 4- and 5- positions (R^3, R^4, R^5, R^6) and in the indicated position on the benzo ring (R^x).

Structures of the the compounds produced in Examples 73-102 are set forth in Tables 3 and 3A.

Examples 80-84

Preparation of 115, 116, 111, 113

Preparation of 4-chloro-3-[4-methoxyphenylmethyl]-nitrobenzene.

In a 500 ml 2-necked rb flask weigh out 68.3 gms phosphorus pentachloride (0.328 mole 1.1 eq). Add 50 mls chlorobenzene. Slowly add 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole). Stir at room temp overnight under N2 then heat 1 hr at 50C.

Remove chlorobenzene by high vacuum. Wash residue with hexane. Dry wt=55.5 gms.

In the same rb flask, dissolve acid chloride (55.5 g 0.25 mole) from above with 100 mls anisole (about 3.4 eq). Chill solution with ice bath while purging with N2. Slowly add 40.3g aluminum chloride (1.2 eq 0.3 mole). Stir under N_2 for 24 hrs.

After 24 hrs, the solution was poured into 300 mls 1N HCl soln. (cold). Stir this for 15 min. Extract several times with diethyl ether. Extract organic layer once with 2% aqueous NaOH then twice with water. Dry organic layer with MgSO4, dry on vac line. Solid is washed well with ether and then ethanol before drying. Wt=34.57g (mixture of meta, ortho and para).

Elemental	theory	found
C	57.65	57.45
H	3.46	5.51
N	4.8	4.8
Cl	12.15	12.16

With the next step of the reduction of the ketone with trifluoromethane sulfonic aid and triethyl silane, crystallization with ethyl acetate/hexane affords pure 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.

4-Chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene was then reacted as specified in the synthesis of 117 and 118 from 2-chloro-4-nitrophenylmethane. From these procedures 115 and 116 can be synthesized. Compounds 111 and 113 can be synthesized from the procedure used to prepare compound 121.

Compound 114 can be prepared by reaction of 116 with ethyl mercaptan and aluminum trichloride.

Examples 85 and 86

Preparation of 117 and 118

2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 5).

The sulfone-aldehyde (31.8 g) was dissolved in ethanol/toluene and placed in a parr reactor with 100 ml toluene and 100 ml of ethanol and 3.2 g of 10% Pd/C and heated to 55 C and 100 psi of hydrogen gas for 14 hours. The reaction was then filtered to remove the catalyst. The amine product (.076 moles, 29.5 g) from this reaction was then reacted with benzyl chloroformate (27.4g) in toluene in the presence of 35 g of potassium carbonate and stirred at room temperature overnight. After work up by extraction with water, the CBZ protected amine product was further purified by precipitation from toluene/hexane.

The CBZ protected amine product was then reacted with 3 equivalents of potassium t-butoxide in THF at 0 C to yield compounds 117 and 118 which were separated by silica gel column chromatography.

Examples 89 and 90

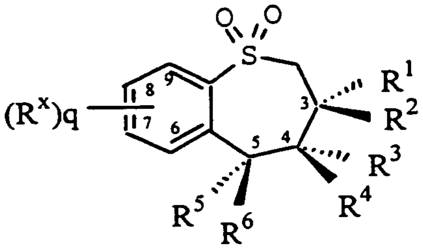
Preparation of 121 or 122

Compound 118 (.013 moles, 6.79g) is dissolved in 135 ml of dry chloroform and cooled to -78 C, next 1.85 ml of boron tribromide (4.9 g) was added and the reaction is allowed to warm to room temperature. Reaction is complete after 1.5 hours. The reaction is quenched by addition of 10% potassium carbonate at 0 C and extract with ether. Removal of ether yields compound 121. A similar procedure can be used to produce 122 from 117.

Examples 93-96

Compounds 126, 127, 128 and 129 as set forth in Table 3 were prepared substantially in the manner described above for compounds 115, 116, 111 and 113, respectively, except that fluorobenzene was used as a starting material in place of anisole.

Table 3: Specific Compounds (#102-111, 113-130, 132-134, 136, 138, 142-144, 262-296)



Cp#	R^1	R^2	R^3	R^4	R^5	R^6	$(R^x)q$
102	Et-	n-Bu-	HO-	H-	Ph-	H-	I$^-$, 7-(CH$_3$)$_3$N$^+$-
103	n-Bu-	Et-	HO-	H-	Ph-	H-	I$^-$, 7-(CH$_3$)$_3$N$^+$-
104	Et-	n-Bu-	HO-	H-	Ph-	H-	7-(CH$_3$)$_2$N-
105	Et-	n-Bu-	HO-	H-	Ph-	H-	7-CH$_3$SO$_2$NH-
106	Et-	n-Bu-	HO-	H-	Ph-	H-	7-Br-CH$_2$-CONH-
107	n-Bu-	Et-	HO-	H-	p-n-C$_{10}$H$_{21}$--O-Ph-	H-	7-NH$_2$-
108	Et-	n-Bu-	HO-	H-	Ph-	H-	7-C$_5$H$_{11}$CONH-
109	Et-	n-Bu-	HO-	H-	p-n-C$_{10}$H$_{21}$--O-Ph-	H-	7-NH$_2$-
110	Et-	n-Bu-	HO-	H-	Ph-	H-	7-CH$_3$CONH-
111	n-Bu-	Et-	HO-	H-	p-HO-Ph-	H-	7-NH$_2$-
113	Et-	n-Bu-	HO-	H-	p-HO-Ph-	H-	7-NH$_2$-

114	Et-	n-Bu-	HO-	H-	p-CH_3O-Ph-	H-	7-NH_2-
115	n-Bu-	Et-	HO-	H-	p-CH_3O-Ph-	H-	7-NH-CBZ
116	Et-	n-Bu-	HO-	H-	p-CH_3O-Ph-	H-	7-NH-CBZ
117	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NH-CBZ
118	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NH-CBZ
119	Et-	n-Bu-	HO-	H-	Ph-	H-	7-$NHCO_2$-t-Bu
120	n-Bu-	Et-	HO-	H-	Ph-	H-	7-$NHCO_2$-t-Bu
121	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NH_2-
122	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NH_2-
123	Et-	n-Bu-	HO-	H-	Ph-	H-	7-n-C_6H_{13}-NH-
124	n-Bu-	Et-	HO-	H-	Ph-	H-	7-n-C_6H_{13}-NH-
125	Et-	n-Bu-	HO-	H-	Ph-	H-	I^-, 8-$(CH_3)_3N^+(CH_2CH_2O)_3$-
126	n-Bu-	Et-	HO-	H-	p-F-Ph-	H-	7-NH-CBZ
127	n-Bu-	Et-	HO-	H-	p-F-Ph-	H-	7-NH_2-
128	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH-CBZ
129	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH_2-
130	Et-	n-Bu-	HO-	H-	Ph-	H-	I^-, 8-$(CH_3)_3N^+C_6H_{12}O$-
132	Et-	n-Bu-	HO-	H-	Ph-	H-	8-phthalimidyl-$C_6H_{12}O$-

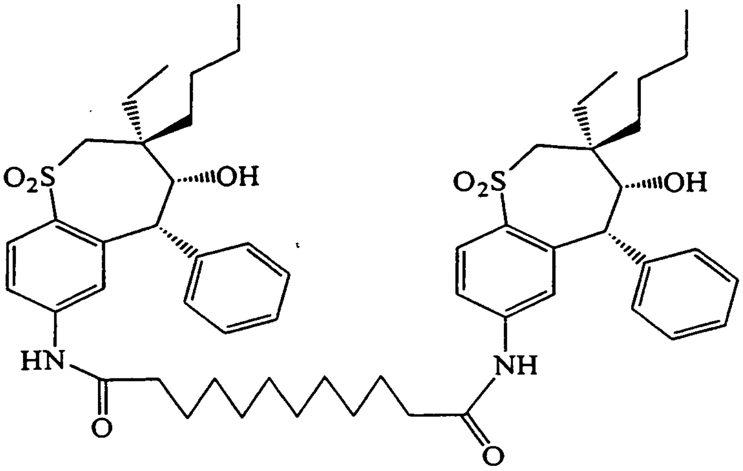
133	Et-	n-Bu-	HO-	H-	Ph-	H-	8-n-$C_{10}H_{21}$-
134	Et-	n-Bu-	HO-	H-	Ph-	H-	8- I-$(C_2H_4O)_3$-
136	Et-	n-Bu-	HO-	H-	Ph-	H-	8- HO-
138	n-Bu-	Et-	HO-	H-	Ph-	H-	8- CH_3CO_2-
142	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-CH_3S-
143	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-CH_3S-
144	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-azetidine
262	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-CH_3O-
263	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-CH_3O-
264	Et-	n-Bu-	HO-	H-	m-CF_3-Ph-	H-	7-CH_3O-
265	Et-	n-Bu-	H-	HO-	H-	m-CF_3-Ph-	7-CH_3O-
266	Et-	n-Bu-	HO-	H-	m-HO-Ph-	H-	7-HO-
267	Et-	n-Bu-	HO-	H-	m-HO-Ph-	H-	7-CH_3O-
268	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH_3O-
269	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-CH_3O-
270	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-HO-
271	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-Br-
272	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-Br-
273	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-F-

274	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-F-
275	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-F-
276	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-F-
277	Et-	n-Bu-	HO-	H-	m-F-Ph-	H-	7-CH_3O-
278	Et-	n-Bu-	H-	HO-	H-	o-F-Ph-	7-CH_3O-
279	Et-	n-Bu-	H-	HO-	H-	m-F-Ph-	7-CH_3O-
280	Et-	n-Bu-	HO-	H-	o-F-Ph-	H-	7-CH_3O-
281	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH_3S-
282	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH_3-
283	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-CH_3-
284	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-morpholine
285	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-pyrrolidine
286	Et-	Et-	HO-	H-	Ph-	H-	7-NH-CBZ-
287	Et-	Et-	HO-	H-	Ph-	H-	7-NH_2-
288	CH_3-	CH_3-	HO-	H-	Ph-	H-	7-NH_2-
289	n-C_3H_7-	n-C_3H_7-	HO-	H-	Ph-	H-	7-NH_2-
290	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-NH_2-
291	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-NH-CBZ-
292	n-Bu-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH_2-
293	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-$PhCH_2N$-
294	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-$(CH_3)_2N$-

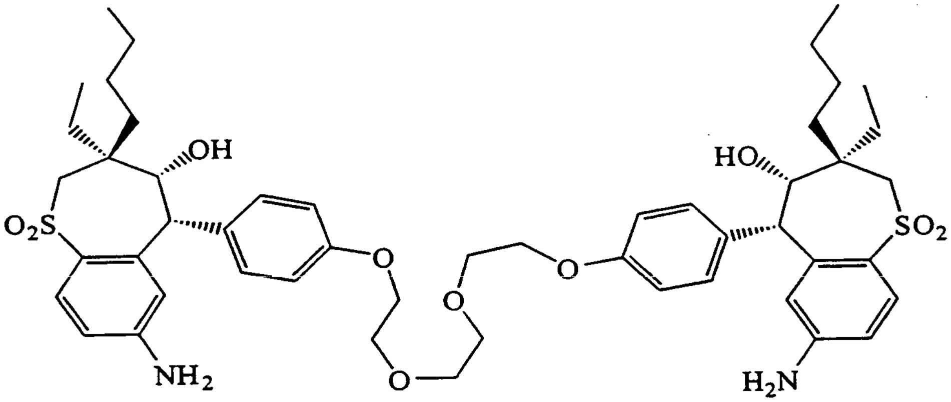
295	Et-	n-Bu-	HO-	H-	p-I-$(C_2H_4O)_3$-Ph-	H-	7-NH_2-
296	Et-	n-Bu-	HO-	H-	I^-, p-$(CH_3)_3N^+(C_2H_4O)_3$-Ph-	H-	7-NH_2-

TABLE 3A

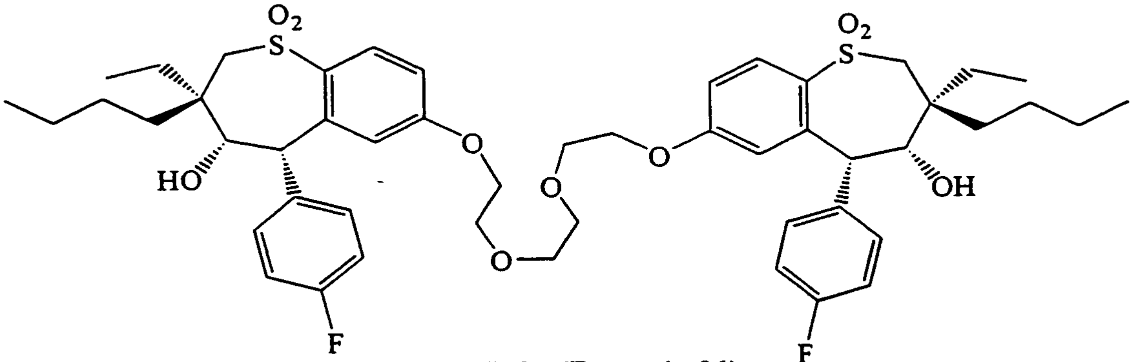
Bridged Benzothiepines (#101, 112, 131, 135, 137, 139-141)



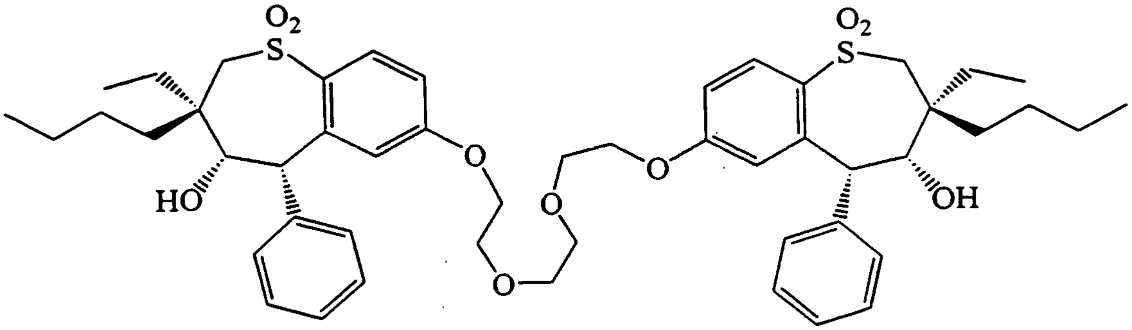
CPD # 101 (Example 59)



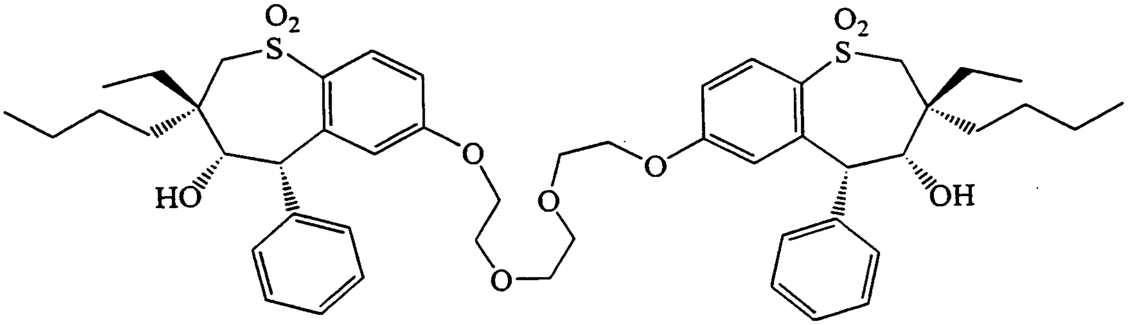
CPD #112 (Example 53)



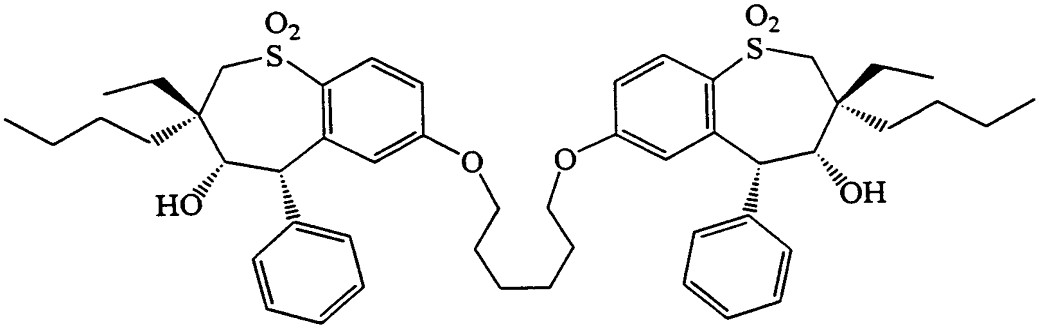
CPD #131 (Example 56)


O2
S
O
O
O
O
HO
OH
O2
S

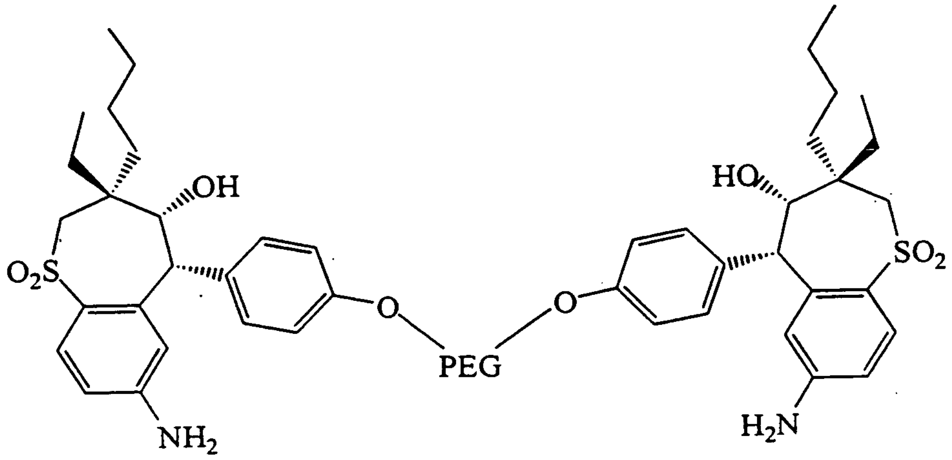
CPD #135 (Example 55)


O2
S
O
O
O
O
HO
OH
O2
S

CPD #137 (Example 57)

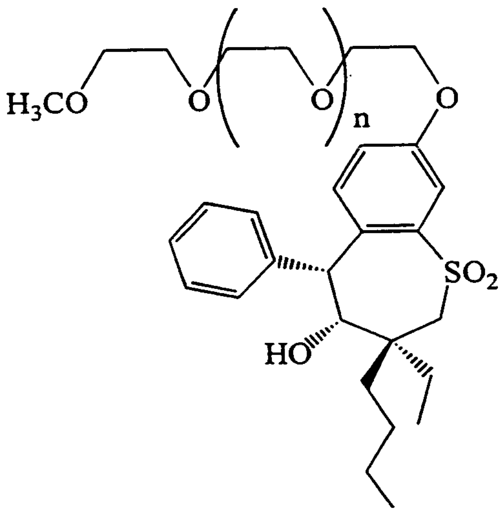

O2
S
O
O
HO
OH
O2
S

CPD #139 (Example 58)



PEG = 3400 molecular weight polyethyleneglycol bridge

CPD #140 (Example 51)

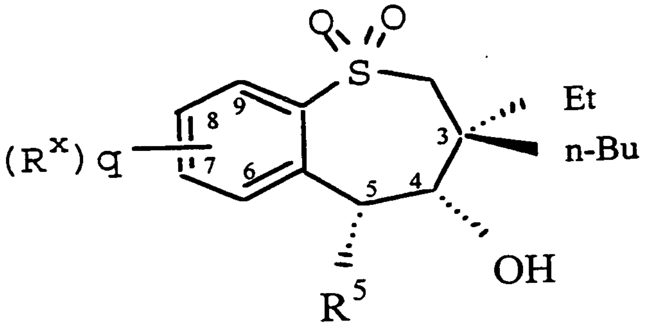


CPD #141 (Example 50)

Examples 104-231

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 4. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5-positions (R^3, R^4, R^5, R^6) and in the indicated position on the benzo ring (R^x).

Table 4: Alternative compounds #1 (#302-312, 314-430)



Cpd#	R^5	(R^x) q
302	p-F-Ph-	7-(1-aziridine)
303	p-F-Ph-	7-EtS-
304	p-F-Ph-	7-$CH_3S(O)$-
305	p-F-Ph-	7-$CH_3S(O)_2$-
306	p-F-Ph-	7-PhS-
307	p-F-Ph-	7-CH_3S- 9-CH_3S-
308	p-F-Ph-	7-CH_3O- 9-CH_3O-
309	p-F-Ph-	7-Et-
310	p-F-Ph-	7-iPr-
311	p-F-Ph-	7-t-Bu-
312	p-F-Ph-	7-(1-pyrazole)-
314	m-CH_3O-Ph	7-(1-azetidine)
315	m-CH_3O-Ph-	7-(1-aziridine)
316	m-CH_3O-Ph-	7-EtS-
317	m-CH_3O-Ph-	7-$CH_3S(O)$-

318	m-CH_3O-Ph-	7-$CH_3S(O)_2$-
319	m-CH_3O-Ph-	7-PhS-
320	m-CH_3O-Ph	7-CH_3S- 9-CH_3S-
321	m-CH_3O-Ph	7-CH_3O- 9-CH_3O-
322	m-CH_3O-Ph	7-Et-
323	m-CH_3O-Ph	7-iPr-
324	m-CH_3O-Ph	7-t-Bu-
325	p-F-Ph-	6-CH_3O- 7-CH_3O- 8-CH_3O-
326	p-F-Ph-	7-(1-azetidine) 9-CH_3-
327	p-F-Ph-	7-EtS- 9-CH_3-
328	p-F-Ph-	7-$CH_3S(O)$- 9-CH_3-
329	p-F-Ph-	7-$CH_3S(O)_2$- 9-CH_3-
330	p-F-Ph-	7-PhS- 9-CH_3-
331	p-F-Ph-	7-CH_3S- 9-CH_3-
332	p-F-Ph-	7-CH_3O- 9-CH_3-
333	p-F-Ph-	7-CH_3- 9-CH_3-
334	p-F-Ph-	7-CH_3O- 9-CH_3O-

335	p-F-Ph-	7-(1-pyrrole)
336	p-F-Ph-	7-(N)N'-methylpiperazine
337	p-F-Ph-	Ph-
338	p-F-Ph-	7-$CH_3C(=CH_2)$-
339	p-F-Ph-	7-cyclpropyl
340	p-F-Ph-	7-$(CH_3)_2NHN$-
341	p-F-Ph-	7-(N)-azetidine 9-CH_3S-
342	p-F-Ph-	7-(N-pyrrolidine) 9-CH_3S-
343	p-F-Ph-	7-$(CH_3)_2N$- 9-CH_3S-
344	m-CH_3O-Ph-	7-(1-pyrazole)
345	m-CH_3O-Ph-	7-(N)N'-methylpiperazine
346	m-CH_3O-Ph-	Ph-
347	m-CH_3O-Ph-	7-$CH_3C(=CH_2)$-
348	m-CH_3O-Ph-	7-cyclopropyl
349	m-CH_3O-Ph-	7-$(CH_3)_2NHN$-
350	m-CH_3O-Ph-	7-(N)-azetidine 9-CH_3S-
351	m-CH_3O-Ph-	7-(N-pyrrolidine)- 9-CH_3S-
352	m-CH_3O-Ph-	7-$(CH_3)_2N$- 9-CH_3S-

353	m-CH_3O-Ph-	6-CH_3O- 7-CH_3O- 8-CH_3O-
354	m-CH_3O-Ph-	7-(1-azetidine) 9-CH_3-
355	m-CH_3O-Ph-	7-EtS- 9-CH_3-
356	m-CH_3O-Ph-	7-$CH_3S(O)$- 9-CH_3-
357	m-CH_3O-Ph-	7-$CH_3S(O)_2$- 9-CH_3-
358	m-CH_3O-Ph-	7-PhS- 9-CH_3-
359	m-CH_3O-Ph-	7-CH_3S- 9-CH_3-
360	m-CH_3O-Ph-	7-CH_3O- 9-CH_3-
361	m-CH_3O-Ph-	7-CH_3- 9-CH_3-
362	m-CH_3O-Ph-	7-CH_3O- 9-CH_3O-
363	thien-2-yl	7-(1-aziridine)
364	thien-2-yl	7-EtS-
365	thien-2-yl	7-$CH_3S(O)$-
366	thien-2-yl	7-$CH_3S(O)_2$-
367	thien-2-yl	7-PhS-
368	thien-2-yl	7-CH_3S- 9-CH_3S-
369	thien-2-yl	7-CH_3O- 9-CH_3O-

370	thien-2-yl	7-Et-
371	thien-2-yl	7-iPr-
372	thien-2-yl	7-t-Bu-
373	thien-2-yl	7-(1-pyrrole)-
374	thien-2-yl	7-CH_3O-
375	thien-2-yl	7-CH_3S-
376	thien-2-yl	7-(1-azetidine)
377	thien-2-yl	7-Me-
378	5-Cl-thien-2-yl	7-(1-azetidine)
379	5-Cl-thien-2-yl	7-(1-aziridine)
380	5-Cl-thien-2-yl	7-EtS-
381	5-Cl-thien-2-yl	7-$CH_3S(O)$-
382	5-Cl-thien-2-yl	7-$CH_3S(O)_2$-
383	5-Cl-thien-2-yl	7-PhS-
384	5-Cl-thien-2-yl	7-CH_3S- 9-CH_3S-
385	5-Cl-thien-2-yl	7-CH_3O- 9-CH_3O-
386	5-Cl-thien-2-yl	7-Et-
387	5-Cl-thien-2-yl	7-iPr-
388	5-Cl-thien-2-yl	7-t-Bu-
389	5-Cl-thien-2-yl	7-CH_3O-
390	5-Cl-thien-2-yl	7-CH_3S-
391	5-Cl-thien-2-yl	7-Me

392	thien-2-yl	7-(1-azetidine) 9-CH_3-
393	thien-2-yl	7-EtS- 9-CH_3-
394	thien-2-yl	7-$CH_3S(O)$- 9-CH_3-
395	thien-2-yl	7-$CH_3S(O)_2$- 9-CH_3-
396	thien-2-yl	7-PhS- 9-CH_3-
397	thien-2-yl	7-CH_3S- 9-CH_3-
398	thien-2-yl	7-CH_3O- 9-CH_3-
399	thien-2-yl	7-CH_3- 9-CH_3-
400	thien-2-yl	7-CH_3O- 9-CH_3O-
401	thien-2-yl	7-(1-pyrazrole)
402	thien-2-yl	7-(N)N'-methylpiperazine
403	thien-2-yl	Ph-
404	thien-2-yl	7-$CH_3C(=CH_2)$-
405	thien-2-yl	7-cyclpropyl
406	thien-2-yl	7-$(CH_3)_2NHN$-
407	thien-2-yl	7-(N)-azetidine 9-CH_3S-
408	thien-2-yl	7-(N-pyrrolidine) 9-CH_3S-
409	thien-2-yl	7-$(CH_3)_2N$- 9-CH_3S-

411	5-Cl-thien-2-yl	7-(1-pyrazrole)
412	5-Cl-thien-2-yl	7-(N)N'-methylpiperazine
413	5-Cl-thien-2-yl	Ph-
414	5-Cl-thien-2-yl	7-$CH_3C(=CH_2)$-
415	5-Cl-thien-2-yl	7-cyclopropyl
416	5-Cl-thien-2-yl	7-$(CH_3)_2NHN$-
417	5-Cl-thien-2-yl	7-(N)-azetidine 9-CH_3S-
418	5-Cl-thien-2-yl	7-(N-pyrrolidine)- 9-CH_3S-
419	5-Cl-thien-2-yl	7-$(CH_3)_2N$- 9-CH_3S-
420	5-Cl-thien-2-yl	7-(1-azetidine) 9-CH_3-
421	5-Cl-thien-2-yl	7-EtS- 9-CH_3-
422	5-Cl-thien-2-yl	7-$CH_3S(O)$- 9-CH_3-
423	5-Cl-thien-2-yl	7-$CH_3S(O)_2$- 9-CH_3-
424	5-Cl-thien-2-yl	7-PhS- 9-CH_3-
425	5-Cl-thien-2-yl	7-CH_3S- 9-CH_3-
426	5-Cl-thien-2-yl	7-CH_3O- 9-CH_3-

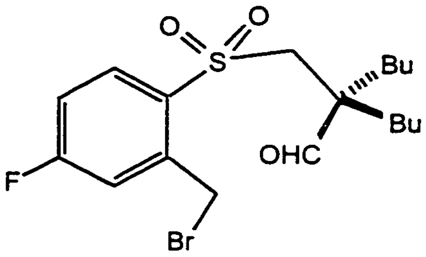
427	5-Cl-thien-2-yl	7-CH_3- 9-CH_3-
428	5-Cl-thien-2-yl	7-CH_3O- 9-CH_3O-
429	thien-2-yl	6-CH_3O- 7-CH_3O- 8-CH_3O-
430	5-Cl-thien-2-yl	6-CH_3O- 7-CH_3O- 8-CH_3O-

Examples 232-1394

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 1. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5-positions (R^3, R^4, R^5, R^6) and in the indicated position on the benzo ring (R^x).

Example 1395

Dibutyl 4-fluorobenzene dialdehyde



Step 1: Preparation of dibutyl 4-fluoro benzene dialdehyde

To a stirred solution of 17.5 g (123 mmol) of 2,5-difluorobenzaldehyde (Aldrich) in 615 mL of DMSO at ambient temperature was added 6.2 g (135 mmol) of lithium sulfide (Aldrich). The dark red solution was stirred at 75 C for 1.5 hours, or until the starting material was completely consumed, and then 34 g (135 mmol) of dibutyl mesylate aldehyde was added at about 50 C. The reaction mixture was stirred at 75 C for three hours or until the reaction was completed. The cooled solution was poured into water and extracted with ethyl acetate. The combined extracts were washed with water several times, dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 23.6 g (59%) of fluorobenzene dialdehyde as a yellow oil: ^1H NMR ($CDCl_3$) d 0.87 (t, *J* = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.78 (m, 4H), 3.09 (s, 2H), 7.2-7.35 (m, 1H), 7.5-7.6 (m, 2H), 9.43 (s, 1H), 10.50 (d, *J* = 2.62 Hz, 1H).

Step 2: Preparation of dibutyl 4-fluorobenzyl alcohol

To a solution of 22.6 g (69.8 mmol) of the dialdehyde obtained from Step 1 in 650 mL of THF at -60 C was added 69.8 mL (69.8 mmol) of DIBAL (1M in THF) via a syringe. The reaction mixture was stirred at -40 C for 20 hours. To the cooled solution at -40 C was added sufficient amount of ethyl acetae to quench the excess of DIBAL, followed by 3 N HCl. The mixture was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 13.5 g (58%) of recovered starting material, and 8.1 g (36%) of the desired fluorobenzyl alcohol as a colorless oil: ^{1}H NMR (CDCl3) d 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.72 (m, 4H), 1.94 (br s, 1H), 3.03 (s, 2H), 4.79 (s, 2H), 6.96 (dt, J = 8.46, 3.02 Hz, 1H), 7.20 (dd, J = 9.47, 2.82 Hz, 1H), 7.42 (dd, J = 8.67, 5.64, 1H), 9.40 (s, 1H).

Step 3: Preparation of dibutyl 4-fluorobenzyl bromide To a solution of 8.1 g (25 mmol) of benzyl alcohol obtained from Step 2 in 100 mL of DMF at -40 C was added 47 g (50 mmol) of bromotriphenyphosphonium bromide (Aldrich). The resulting solution was stirred cold for 30 min, then was allowed to warm to 0 C. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed a few times with water, dried (MgSO4), and concentrated in vacuo. The mixture was stirred in small amount of ethyl acetate/hexane mixture (1:4 ratio) and filtered through a pad of silica gel, eluting with same solvent mixture. The combined filtrate was concentrated in vacuo to give 9.5 g (98%) of the desired product as a colorless oil: ^{1}H NMR (CDCl3) d 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.55-1.78 (m, 4H), 3.11 (s, 2H), 4.67 (s, 2H), 7.02 (dt, J = 8.46, 3.02 Hz, 1H), 7.15 (dd, J = 9.47, 2.82 Hz, 1H), 7.46 (dd, J = 8.67, 5.64, 1H), 9.45 (s, 1H).

Step 4: Preparation of sulfonyl 4-fluorobenzyl bromide

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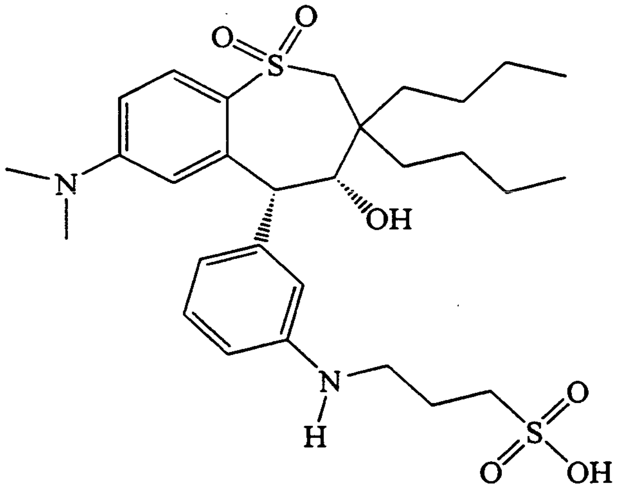
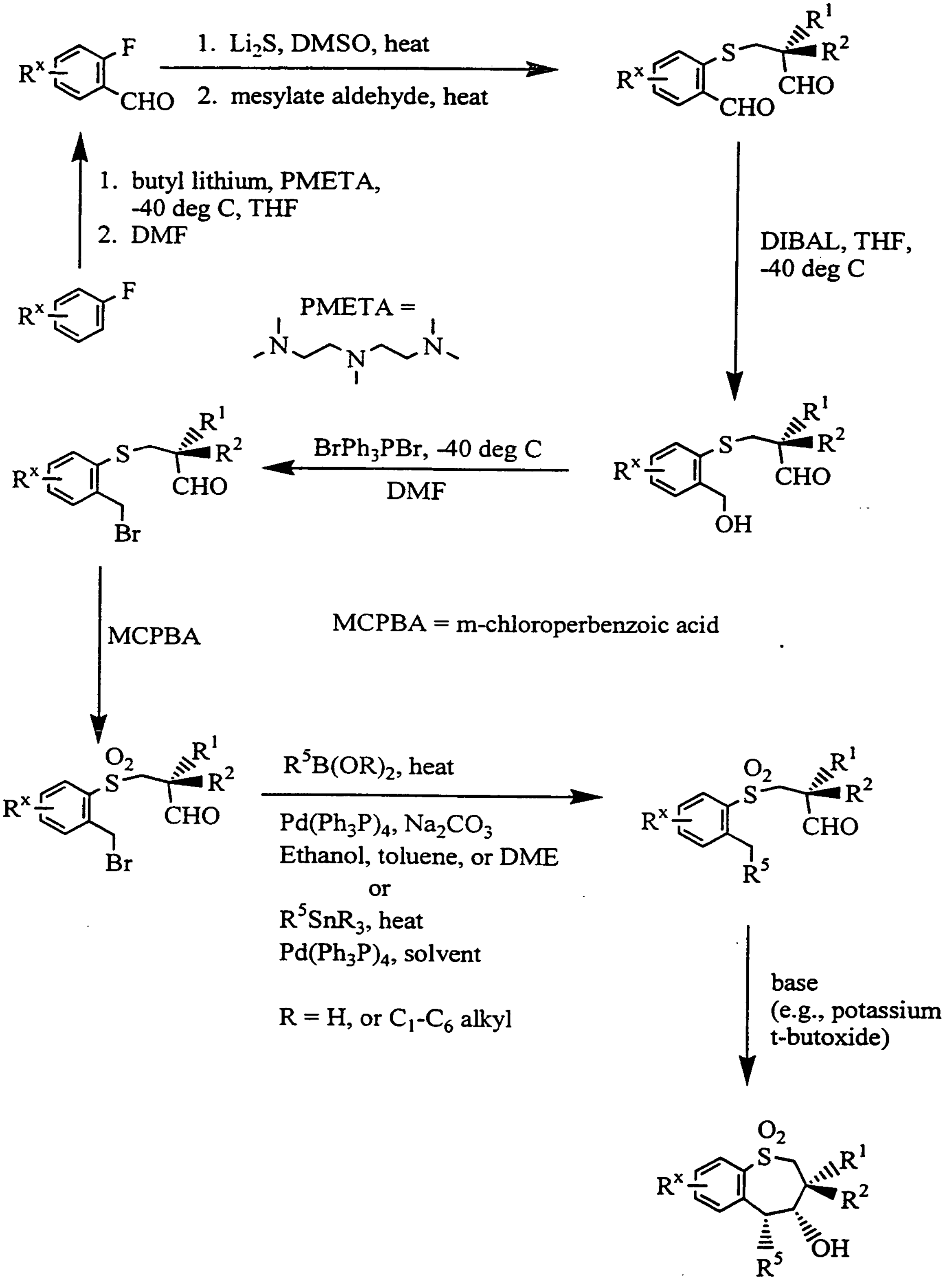
To a solution of 8.5 g (25 mmol) of sulfide obtained from Step 3 in 200 mL of CH_2Cl_2 at 0 ^{0}C was added 15.9 g (60 mmol) of mCPBA (64% peracid). The resulting solution was stirred cold for 10 min, then was allowed to stirred ambient temperature for 5 hours. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed several times with saturated Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo to give 10.2 g (98%) of the desired product as a colorless oil: ^{1}H NMR ($CDCl_3$) d 0.91 (t, *J* = 7.05 Hz, 6H), 1.03-1.4 (m, 8H), 1.65-1.82 (m, 2H), 1.90-2.05 (m, 2H), 3.54 (s, 2H), 5.01 (s, 2H), 7.04-7.23 (m, 1H), 7.30 (dd, *J* = 8.87, 2.42 Hz, 1H), 8.03 (dd, *J* = 8.86, 5.64, 1H), 9.49 (s, 1H).

Example 1396



Generic Scheme X


F
CHO
R^x
1. Li_2S, DMSO, heat
2. mesylate aldehyde, heat
S
R^1
R^2
CHO
CHO
1. butyl lithium, PMETA, -40 deg C, THF
2. DMF
DIBAL, THF, -40 deg C
PMETA =
N
N
N
BrPh$_3$PBr, -40 deg C
DMF
Br
OH
MCPBA
MCPBA = m-chloroperbenzoic acid
O_2
$R^5B(OR)_2$, heat
$Pd(Ph_3P)_4$, Na_2CO_3
Ethanol, toluene, or DME
or
R^5SnR_3, heat
$Pd(Ph_3P)_4$, solvent
R = H, or C_1-C_6 alkyl
R^5
base
(e.g., potassium t-butoxide)
OH

Generic Scheme X: The nucleophilic substitution of an appropriately substituted 2-fluorobenzaldehyde with lithium sulfide or other nucleophilic sulfide anion in polar solvent (such as DMF, DMA, DMSO ..etc), followed by the addition of dialkyl mesylate aldehyde (**X**), provided a dialkyl benzene dialdehyde **Y**. DIBAL reduction of the dialdehyde at low temperature yielded benzyl alcohol monoaldehyde **Z**. Conversion of benzyl alcohol to benzyl bromide, followed by oxidation of sulfide to sulfone yielded the key intermediate **W**.

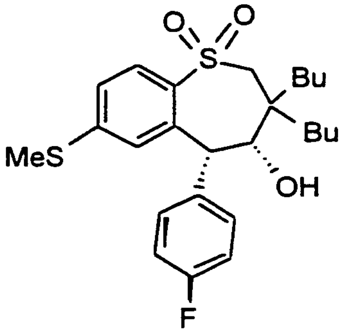
Preparation of N-propylsulfonic acid

To a solution of 51 mg (111 µm) Compound X in ethanol (400 µl) was added 1,3 propane sultone (19.5 µl, 222 µm). The reaction was stirred in a sealed vial at 55 °C for 25 hr. Sample was concentrated under a nitrogen stream and purified by reversed phase chromatography using acetonitrile/water as eluent (30-45%) and afforded the desired material as an off-white solid (28.4 mg, 44%): ^{1}H NMR ($CDCL_3$) d 0.82-0.96 (m, 6H), 1.11-1.52 (m of m, 10H), 1.58-1.72 (m, 1H), 2.08-2.21 (m, 1H), 2.36-2.50 (m, 2H), 2.93 (s, 6H), 3.02-3.22 (m of m, 5H), 3.58-3.76 (m, 2H), 4.15 (s, 1H), 5.51 (s, 1H), 6.45-6.58 (m, 1H), 6.92-7.02 (m, 1H), 7.35-7.41 (m, 1H), 7.41-7.51 (m, 2H), 8.08 (d, *J* = 8.1 Hz, 1H), 8.12-8.25 (m, 1H); MS ES- M-H *m/z* 579.

Example 1397

The 7-fluoro, 9-fluoro and 7,9-difluoro analogs of benzothiepine compounds of this invention can be reacted with sulfur and nitrogen nucleophiles to give the corresponding sulfur and nitrogen substituted analogs. The following example demonstrates the synthesis of these analogs.

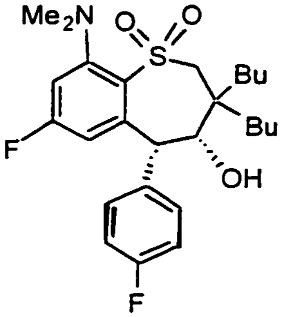
3,3-Dibutyl-5a-(4′-fluorophenyl)-4a-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.

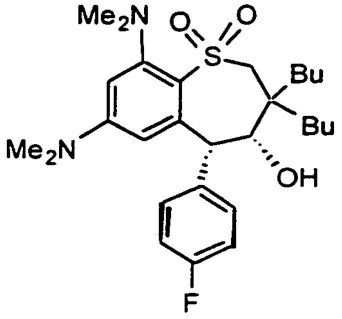


A mixture of 0.4 g 0f 3,3-dibutyl-7-fluoro-5a-(4′-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by previously described method, 0.12 g of sodium methanethiolate and 20 ml of DMF was stirred at 50 C for 3 days. An additional 0.1 g of sodium methanethiolate was added to the reaction mixture and the mixture was stirred for additional 20 h at 50 C then was concentrated in vacuo. The residue was triturated with water and extracte wiith ether. The ether extract was dried over $MgSO_4$ and concentrated in vacuo to 0.44 g of an oil. Purification by HPLC (10% EtOAc in hexane) gave 0.26 g of needles, mp 164-165.5 %C.

3,3-Dibutyl-9-dimethylamino-7-fluoro-5a-(4′-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide and 7,9-

Bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.

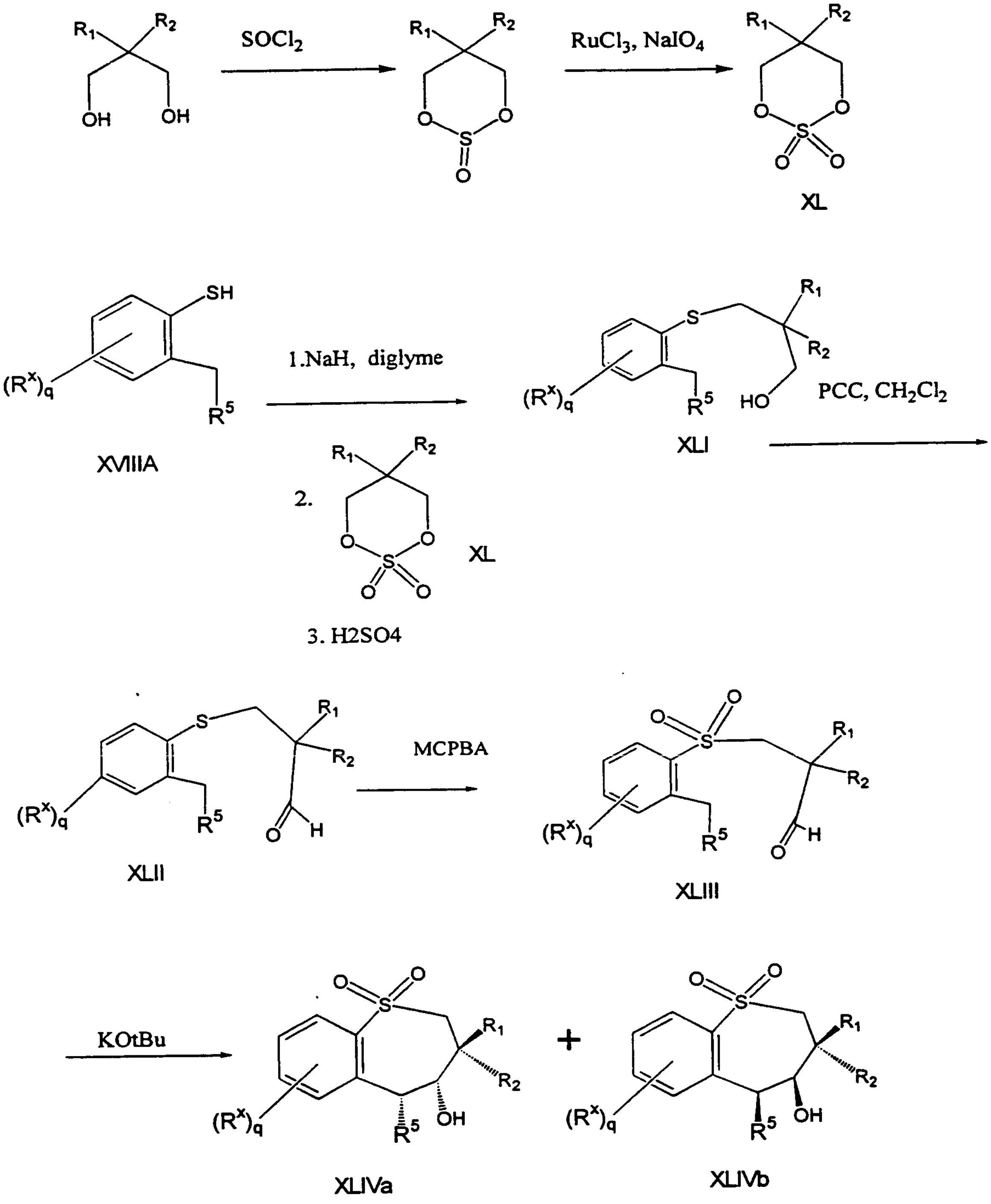




A solution of 0.105 g of 3,3-dibutyl-7,9-difluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by the method described previously, in 20 ml of 2 N dimethylamine in THF was heated at 160 C in a sealed Parr reactor overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with 25 ml of water and extracted with ether. The ether extract was dried over $MgSO_4$ and concentrated in vacuo. The resdue was purified by HPLC (10% EtOAc in hexane) to give 35 mg of an earlier fraction which was identified as 3,3-dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 480 (M^+ +1), and 29 mg of a later fraction which was identified as 7,9-bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 505 (M^+ +1).

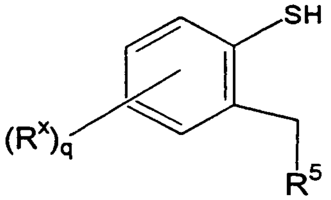
The compounds of this invention can also be synthesized using cyclic sulfate (XL, below) as the reagent as shown in the following schemes XI and XII. The following examples describe a procedure for using the cyclic sulfate as the reagent.

SCHEME XI.


R1
R2
OH
OH
SOCl2
O
S
RuCl3, NaIO4
XL
SH
(R^x)q
R5
XVIIIA
1.NaH, diglyme
2.
XL
3. H2SO4
S
HO
XLI
PCC, CH2Cl2
H
XLII
MCPBA
XLIII
KOtBu
+
XLIVa
XLIVb

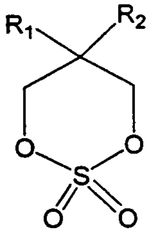
Scheme XI illustrates yet another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl analogs, starting from the thiophenol XVIIIA. Thiophenol XVIIIA can be reacted with cyclic sulfate XL to give the alcohol XLI which can be oxidized to yield the aldehyde XLII. Aldehyde XLII itself can be further oxidized to give the sulfone XLIII which can be cyclized to give a stereoisomeric mixture of benzothiepine XLIVa and XLIVb.

Thiophenol XVIIIA can be prepared according to Scheme 3 as previously discussed and has the following formula:



XVIIIA

wherein R^5, R^x and q are as previously defined for the compounds of formula I. Cyclic sulfate XL can be prepared according to synthetic procedures known in the art and has the following formula:



XL

wherein R^1 and R^2 are as previously defined for the compounds of formula I. Preferably, R^1 and R^2 are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^1 and R^2 are n-butyl.

In the process of Scheme XI, thiophenol XVIIIA is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as methoxyethyl ether. While the reaction conditions such as temperature and time are not narrowly critical, the reaction preferably is allowed to proceed at about room temperature for about two hours. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield can be improved by using about 1.01 to 1.3 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIA present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIA present.

In the process of the invention, thiophenol XVIIIA also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing thiophenol XVIIIA prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the hydrogen atom from the mercaptan group attached to the benzene ring of thiophenol XVIIIA. The resulting sulfur anion of the thiophenol then reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the thiophenol then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group.

The abstracting agent generally is a base having a pH greater than about 10. Preferably, the base is an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; more preferably, the base is sodium hydride. A slight excess of abstracting agent is preferred relative to thiophenol XVIIIA.

Reaction time and yield is improved by using about 1.0 to about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA present. More preferably, this ratio is about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA present.

The sulfate group of the intermediate product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield alcohol XLI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid.

The several reactions involving thiophenol XVIIIA, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need for isolation of any of the intermediates produced.

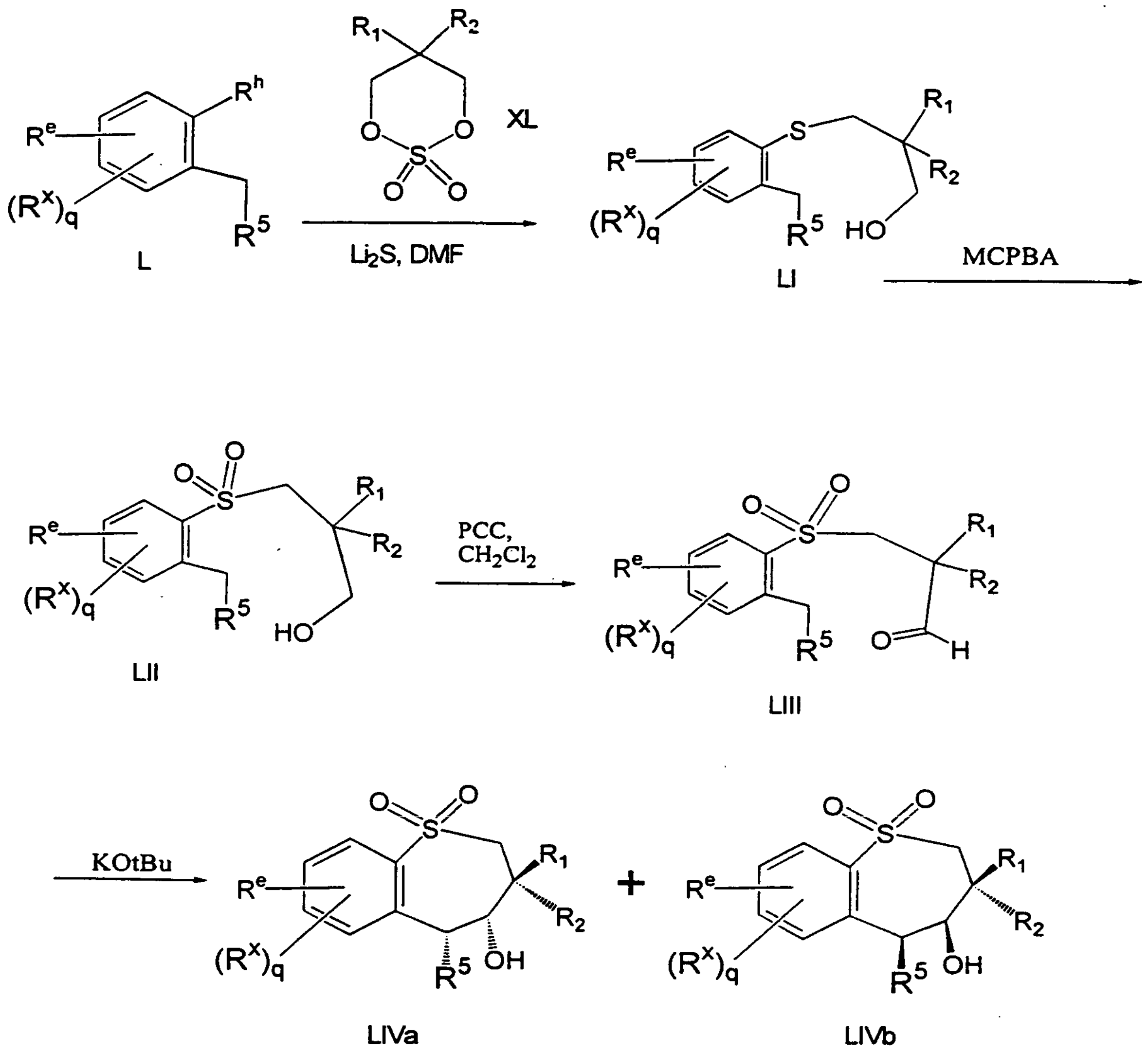
Alcohol XLI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to aldehyde XLII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

Aldehyde XLII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde XLIII. Preferably, the oxidizing agent is metachloroperbenzoic acid.

Sulfone-aldehyde XLIII likewise is isolated by conventional methods and then cyclized to form the stereoisomeric benzothiepines XLIVa and XLIVb. The cyclizing agent preferably is a base having a pH between about 8 and about 9. More preferably, the base is an alkoxide base, and still more preferably, the base is potassium tert-butoxide.

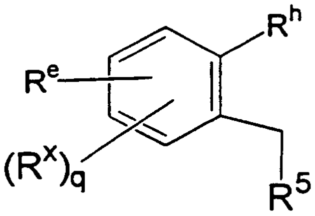
The two oxidation steps of Scheme XI can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield a sulfone-alcohol which is then oxidized to yield a sulfone-aldehyde.

Scheme XII


L
XL
Li2S, DMF
LI
MCPBA
LII
PCC, CH2Cl2
LIII
KOtBu
LIVa
LIVb

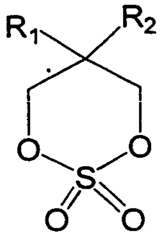
Scheme XII illustrates still another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl analogs, starting from the halobenzene L. Halobenzene L can be reacted with cyclic sulfate XL disclosed above to give the alcohol LI which can be oxidized to yield the sulfone-alcohol LII. Sulfone-alcohol LII itself can be further oxidized to give the sulfone-aldehyde LIII which can be cyclized to give a stereoisomeric mixture of benzothiepine LIVa and LIVb.

Halobenzene L (which is commercially available or can be synthesized from commercially available halobenzenes by one skilled in the art) has the following formula:



L

wherein R^5, R^x, and q are as previously defined for the compounds of formula I; R^h is a halogen such as chloro, bromo, fluoro or iodo; and R^e is an electron withdrawing group at the ortho or para position of the halobenzene, and is preferably a p-nitro or o-nitro group. Cyclic sulfate XL can be prepared as set forth in Scheme XI and can have the following formula:



XL

wherein R^1 and R^2 are as previously defined for the compounds of formula I. Preferably, R^1 and R^2 are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^1 and R^2 are n-butyl.

In the process of Scheme XII, halobenzene L is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as dimethyl formamide or N:N-dimethylacetamide, and more preferably, in dimethyl formamide. Although the reaction conditions such as temperature and time are not narrowly critical, the reaction preferably is allowed to proceed at between about 70°C and about 90°C for about 8 to 12 hours. More preferably, the reaction temperature is maintained at about 80°C. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield is improved by using about 1.1 to 1.3 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present.

In the process of the invention, halobenzene L also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing halobenzene L prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the halogen atom attached to the benzene ring of halobenzene L and replaces that atom with a divalent sulfur atom. The resulting sulfur anion reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the halobenzene then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group. The abstracting agent generally is a dialkali metal sulfide, and preferably it is dilithium sulfide. A slight excess of the abstracting agent is preferred relative to halobenzene L. Reaction time and yield is improved by using about 1.01 to 1.3 equivalents of abstracting agent for each equivalent of halobenzene L present. More preferably, this ratio is about 1.05 equivalents of abstracting agent for each equivalent of halobenzene L present.

The sulfate group of the product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield a mixture of an ester and alcohol LI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid. The ester is then converted to alcohol LI by treatment with an alkali metal hydroxide, preferably sodium hydroxide.

The several reactions involving halobenzene L, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need to isolate any of the intermediates produced.

Alcohol LI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to sulfone-alcohol LII. Preferably, the oxidizing agent is metachloroperbenzoic acid. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

Sulfone-alcohol LII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde LIII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

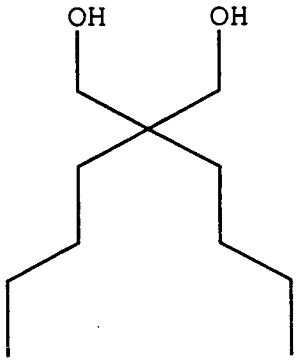
Sulfone-aldehyde XLIII is then converted to the desired benzothiepine-1,1-dioxides according to the procedure previously set forth in Scheme XI.

The two oxidation steps can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield an aldehyde which is then oxidized to yield a sulfone-aldehyde.

Use of the cyclic sulfate reagent instead of a mesylate reagent in Schemes XI and XII improves the overall yield and avoids many of the purification difficulties encountered relative to those reaction schemes proceeding through a mesylate intermediate. Overall yields are significantly improved when a cyclic sulfate is used instead of a mesylate reagent. In addition, chromatographic separation of the intermediate product of the cyclic sulfate coupling step of the reaction is not necessary. For example, in Schemes XI and XII the intermediate is a water soluble alkali metal salt and the impurities can be removed by extraction with ether. The intermediate is then hydrolyzed to the desired alcohol.

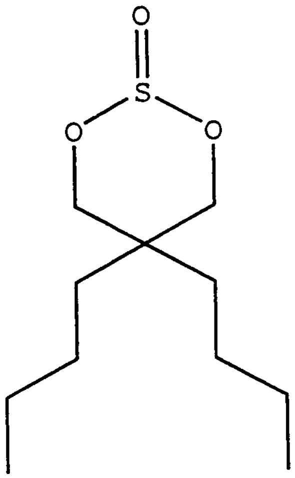
Example Corresponding to Scheme XI:

Step 1: Preparation of 2,2-dibutyl-1,3-propanediol:



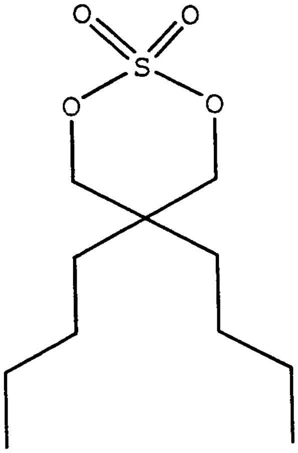
Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyl-diethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated under vacuum to give 98.4 g (yield 95%) of the diol as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 2: Dibutyl-cyclic-sulfite:



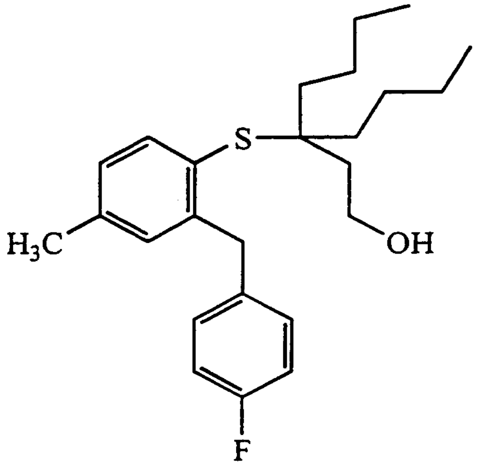
A solution of the dibutyl-diol of step 1 (103 g, 0.5478 mol) in anhydrous methylene chloride (500 ml) and triethylamine (221 g, 4 equivalents, 2.19 mol) was stirred at 0°C under nitrogen. Thionyl chloride (97.78 g, 0.82 mol) was added dropwise to the mixture. Within 5 minutes the solution turned to yellow and then to black when the addition was completed within about half an hour. The reaction was completed within 3 hours (gas chromatography confirmed no starting material was left). The mixture was washed with ice water twice, and brine twice. The organic phase was dried over magnesium sulphate and concentrated under vacuum to give 128 g (yield 100%) of the dibutyl-cyclic-sulfite as a black oil. NMR and MS were consistent with the product.

Step 3: Dibutyl-cyclic sulfate:



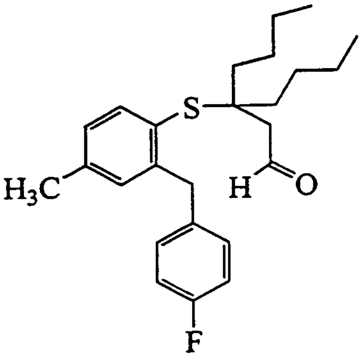
To a solution of the dibutyl-cyclic-sulfite of step 2 (127.5 g, 0.54 mol) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium(III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. Gas chromatography confirmed there was no starting material left. The mixture was extracted once with 300 ml of ether and three times with brine. The organic phase was dried over magnesium sulphate and passed through celite. The filtrate was concentrated under vacuum and gave 133 g (yield 97.8%) of the dibutyl-cyclic-sulfate as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 4: 2-[(2-4'-fluorobenzyl-4-methylphenylthio) methyl]-2-butylhexanol:



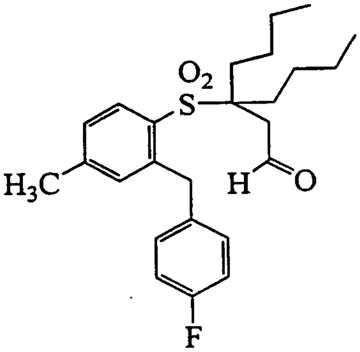
A 60% oil dispersion of sodium hydride (0.27 g, 6.68 mmole) was washed with hexane. The hexane was decanted and 20 ml of methoxyethyl ether was added to the washed sodium hydride and cooled in an ice bath. A mixture of diphenylmethane thiophenol (1.55 g, 6.68 mmole) in 10 ml of methoxyethyl ether was added dropwise over a period of 15 minutes. A mixture of the dibutyl-cyclic-sulfate of step 3 (2.17 g, 8.66 mmole) in 10 ml of methoxyethyl ether was then added. The resulting mixture was stirred for 30 minutes at 0°C and 1 hour at room temperature under nitrogen. Gas chromatography confirmed there was no thiol left. The solvent was evaporated and washed with water and ether two times. The water layer was separated and 20 ml of 10% NaOH was added. This aqueous mixture was boiled for 30 minutes, cooled, acidified with 6N HCI, and boiled for 10 minutes. The mixture was cooled and extracted with ether. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum to give 2.47 g (yield 92.5%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

Step 5: 2-[(2-4'-fluorobenzyl-4-methylphenylthio)methyl]-2-butylhexanal:



To a solution of the hexanol of step 4 (2 g, 4.9 mmole) in 40 ml of methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmole). The reaction mixture was stirred for 3 hours and filtered through silica gel. The filtrate was concentrated under vacuum to give 1.39 g (yield 70%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

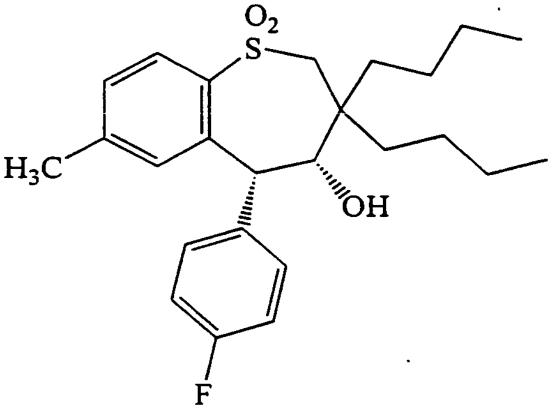
Step 6: 2-[(2-4'-fluorobenzyl-4-methylphenylsulfonyl)methyl]-2-butylhexanal



To a solution of the hexanal of step 5 (0.44 g, 1.1 mmole) in 20 ml of methylene chloride cooled by an ice bath under nitrogen was added 70 % metachloroperbenzoic acid (0.54 g, 2.2 mmole). The reaction mixture was stirred for 18 hours and filtered.

The filtrate was washed successively with 10% NaOH(3X), water, and brine, dried over magnesium sulphate, and concentrated under vacuum to give 0.42 g (yield 90%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

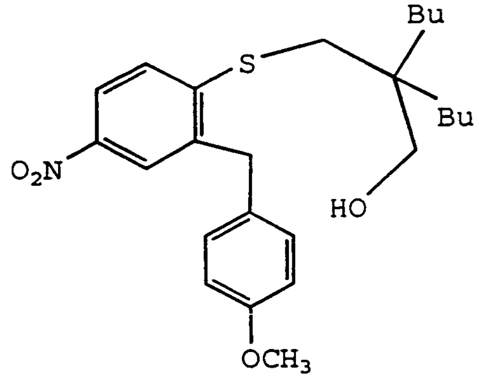
Step 7: Cis-3,3-dibutyl-7-methyl-5-(4'-fluoro-phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide:



A mixture of the hexanal of step 6 (0.37 g, 0.85 mmole) in 30 ml of anhydrous THF was stirred in an ice bath at a temperature of about 0° C. Potassium-tert-butoxide (102 mg, 0.85 mmole) was then added. After 3 hours thin layer chromatography confirmed the presence of the product and a small amount of the starting material. The crude reaction mixture was acidified with 10% HCl, extracted with ether, washed successively with water and brine, dried with $MgSO_4$, and concentrated under vacuum. This concentrate was purified by HPLC (10% EtOAc-Hexane). The first fraction came as 0.1 g of the starting material in the form of an oil. The second fraction yielded 0.27 g (75% yield) of the desired benzothiepine as a white solid. Proton NMR, carbon NMR and MS confirmed the product. (M+H=433).

Example Corresponding to Scheme XII

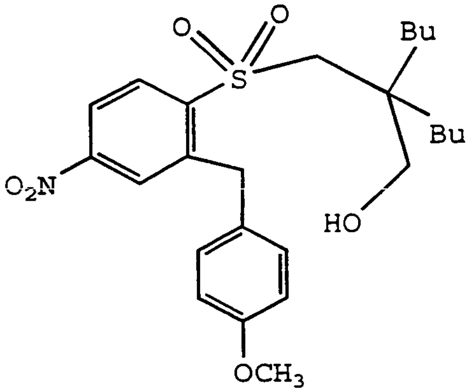
Step 1: 2-[(2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanol:



Chlorodiphenylmethane (10g) was dissolved in 25 ml of DMF and lithium sulfide [1.75 g, 1.05 equivalents] was added. The solution color changed to red. The reaction mixture was heated at 80°C overnight. The solution was cooled to 0°C and dibutyl-cyclic-sulfate (9.9g; prepared as set forth in Step 3 of the Scheme XI examples) in 10 ml of DMF was added and stirred at room temperature overnight. The solvent was evaporated and washed successively with water and ether (three times). The water layer was separated and 40 ml of concentrated sulfuric acid was added and the reaction mixture boiled overnight. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum. The product was boiled with 3M of NaOH for 1 hour. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20%

ethyl acetate and hexane, and concentrated under vacuum to give 11.9 g (yield 74%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

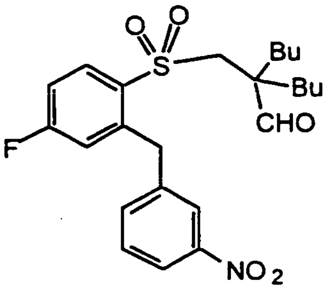
Step 2: 2-[2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanal:



To a solution of the hexanol of step 1 (6 g, 13 mmole) in 50 ml methylene chloride cooled in ice bath under nitrogen was added 70% MCPBA (8.261 g, 33 mmole). The reaction was stirred for 18 hours at room temperature and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under vacuum to give 5 g (yield 77.7%) of the hexanal as a white solid, MP 58-60°C. Proton NMR, C13-NMR and MS confirmed the product.

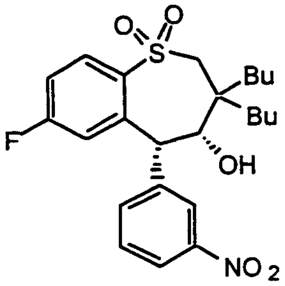
Example 1398

Step 1. Preparation of **2**



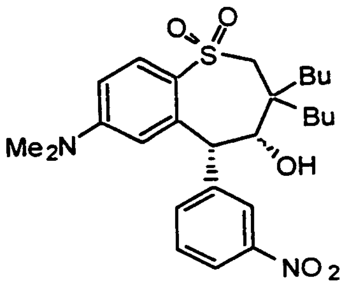
To a solution of 6.0 g of dibutyl 4-fluorobenzene dialdehyde of Example 1395 (14.3 mmol) in 72 mL of toluene and 54 mL of ethanol was added 4.7 g 3-nitrobenzeneboronic acid (28.6 mmol), 0.8 g of tetrakis (triphenylphosphine) palladium(0) (0.7 mmol) and 45 mL of a 2 M solution of sodium carbonate in water. This heterogeneous mixture was refluxed for three hours, then cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-2000) using ethyl acetate/hexanes (25/75) gave 4.8 g (73%) of the title compound as a yellow solid. ^1H NMR ($CDCl_3$) d 0.88 (t, J = 7.45 Hz, 6H), 0.99-1.38 (m, 8H), 1.62-1.75 (m, 2H), 1.85-2.00 (m, 2H), 3.20 (s, 2H), 4.59 (s, 2H), 6.93 (dd, J = 10.5 and 2.4 Hz, 1H), 7.15 (dt, J = 8.4 and 2.85 Hz, 1H), 7.46-7.59 (m, 2H), 8.05-8.16 (m, 3H), 9.40 (s, 1H).

Step 3. Preparation of **3**



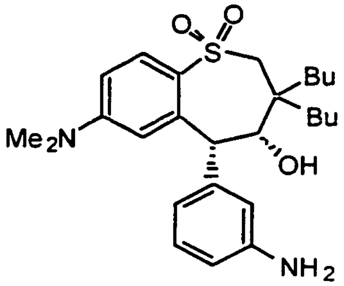
A solution of 4.8 g (10.4 mmol) of **2** in 500 mL THF was cooled to 0 °C in an ice bath. 20 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirring was continued for 30 minutes, then the reaction was quenched with 100 mL of saturated ammonium chloride. The mixture was partitioned between ethyl acetate and water; the organic layer was washed with brine, then dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel chromatography through a 100 ml plug using CH_2Cl_2 as eluent yielded 4.3 g (90%) of **3** as a pale yellow foam. ^1H NMR ($CDCl_3$) d 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 (q_{AB}, J_{AB} = 15.0 Hz, ΔV = 33.2 Hz, 2H), 4.17 (d, J = 6.0 Hz, 1H), 5.67 (s, 1H), 6.34 (dd, J=9.6 and 3.0 Hz, 1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 9.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). MS(FABH$^+$) m/e (relative intensity) 464.5 (100), 446.6 (65). HRMS calculated for M+H 464.1907. Found 464.1905.

Step 4. Preparation of **4**



To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of **3** in 30 ml THF contained in a stainless steel reaction vessel was added 8.2 g dimethyl amine (182 mmol). The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-2000) using an ethyl acetate/hexanes gradient (10-40% ethyl acetate) gave 4.0 g (88%) of **4** as a yellow solid. ^{1}H NMR ($CDCl_3$) d 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.0 Hz, DV= 45.6 Hz, 2H), 4.90 (d, J = 9.0 Hz, 1H), 5.65 (s, 1H), 5.75 (d, J = 2.1 Hz, 1H), 6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 8.20 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (s, 1H). MS($FABH^+$) m/e (relative intensity) 489.6 (100), 471.5 (25). HRMS calculated for M+H 489.2423. Found 489.2456.

Step 5. Preparation of **5**

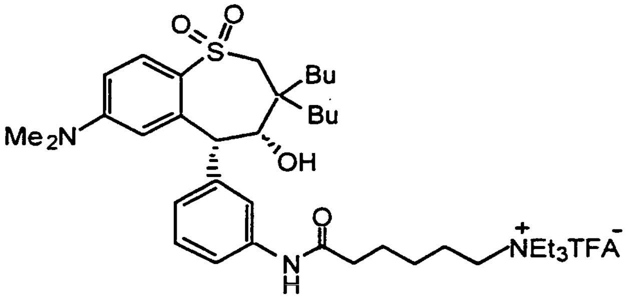


To a suspension of 1.0 g (2.1 mmol) of **4** in 100 ml ethanol in a stainless steel Parr reactor was added 1 g 10% palladium on carbon. The reaction vessel was sealed, purged twice with H_2, then charged with H_2 (100 psi) and heated to 45 °C for six hours. The reaction vessel was cooled to ambient temperature and the contents filtered to remove the catalyst. The filtrate was concentrated in vacuo to give 0.9 g (96%) of **5**. ^1H NMR ($CDCl_3$) d 0.80-0.98 (m, 6H), 1.00-1.52 (m, 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 (s, 2H), 4.14 (s, 1H), 5.43 (s, 1H), 6.09 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, J = 7.8 and 1.8 Hz, 1H), 6.83 (s, 1H), 6.93 (d, J = 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H). MS($FABH^+$) m/e (relative intensity) 459.7 (100). HRMS calculated for M+H 459.2681. Found 459.2670.

Step 6. Preparation of **6**

To a solution of 914 mg (2.0 mmol) of **5** in 50 ml THF was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride. Next was added 4 g (39.6 mmol) TEA. The reaction was stirred 10 minutes, then partitioned between ethyl acetate and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel chromatography through a 70 ml MPLC column using a gradient of ethyl acetate(20-50%) in hexane as eluent yielded 0.9 g (73%) of **6** as a pale yellow oil. ^{1}H NMR (CDCl$_3$) d 0.84-0.95 (m, 6H), 1.02-1.53 (m, 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 (q$_{AB}$, J$_{AB}$ = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 4.10 (s, 1H), 5.51 (s, 1H), 5.95 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.3 and 2.7 Hz, 1H), 7.28 (s, 1H), 7.32-7.41 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H).

Step 7. Preparation of **7**

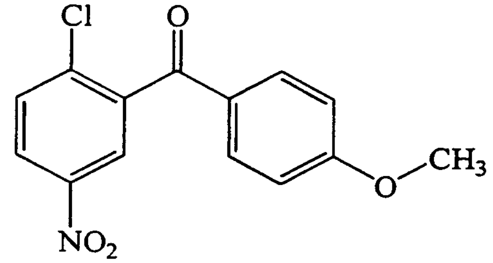


To a solution of 0.9 g (1.45 mmol) of **6** in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated _in vacuo_. Purification by reverse-phase silica gel chromatography (Waters Delta Prep 3000) using an acetonitrile /water gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of **7** as a white foam. ^{1}H NMR (CDCl$_3$) d 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (q$_{AB}$, J$_{AB}$ = 15.6 Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J =

1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed 642.4343.

Example 1398a

Step 1



$C_{14}H_{10}ClNO_4$ fw=291.69

In an inert atmosphere, weigh out 68.3 gms phosphorus pentachloride (0.328mole Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Fit flask with a N_2 inlet adapter and suba seal. Remove from inert atmosphere and begin N_2 purge. Add 50mls anhydrous chlorobenzene (Aldrich 28,451-3) to the PCl_5 via syringe and begin stirring with magnetic stir bar.

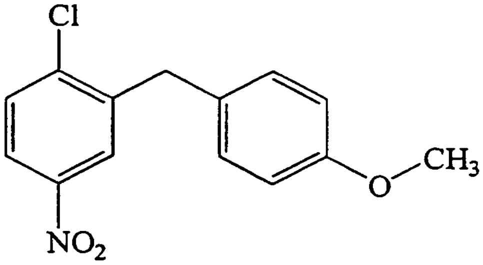
Weigh out 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3). Slowly add to the chlorobenzene solution while under N_2 purge. Stir at room temperature overnight. After stirring at room temperature for ~20hrs, place in oil bath and heat at 50C for 1hr. Remove chlorobenzene by high vacuum. Wash residue with anhydrous hexane. Dry acid chloride wt=61.95gms. Store in inert and dry atmosphere.

In inert atmosphere, dissolve acid chloride with 105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask.

Weigh out 45.1gms aluminum chloride (0.34 moles Aldrich 29,471-3) and place in a solid addition funnel. Fit reaction flask with addition funnel and a N_2 inlet adapter. Remove from inert atmosphere. Chill reaction solution with ice bath and begin N_2 purge. Slowly add $AlCl_3$ to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight .

Quench reaction by pouring into a solution of 300 mls 1N HCl and ice. Stir 15 min. Extract twice with ether. Combine organic layers and extract twice with 2% NaOH, then twice with deionized H_2O. Dry with $MgSO_4$, filter and rotovap to dryness. Remove anisole by high vacuum. Crystalize product from 90% ethanol 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms. Yield 41%. Obtain NMR and mass spec (m/z=292).

Step 2



$C_{14}H_{12}ClNO_3$ fw=277.71

Dissolve 38.10gms (0.131 moles) of the benzophenone from step 1 in 250mls anhydrous methylene chloride. Place in a 3 liter flask fitted with N_2 inlet, addition funnel and stopper. Stir with magnetic stir bar. Chill solution with ice bath.

Prepare a solution of 39.32 gms trifluoromethane sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. Stir 5 minutes after addition is complete.

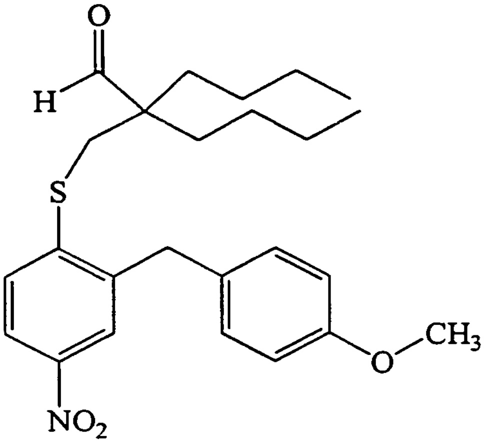
Prepare a solution of 22.85 gms triethyl silane (0.197mole Aldrich 23,019-7) and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. Stir 5 minutes after addition is complete.

Prepare a second solution of 39.32 gms trifluoromethane sulfonic acid and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. Stir 5 minutes after addition is complete.

Prepare a second solution of 22.85 gms triethyl silane and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. After all additions are made allow to slowly warm to room temperature overnight. Stir under N_2 overnight.

Prepare 1300 mls saturated $NaHCO_3$ in a 4 liter beaker. Chill with ice bath. While stirring vigorously, slowly add reaction mixture. Stir at chilled temperature for 30 min. Pour into a separatory funnel and allow separation. Remove organic layer and extract aqueous layer 2 times with methylene chloride. Dry organic layers with $MgSO_4$. Crystallize from ethanol. Dry on vacuum line. Dry wt=28.8gms. Confirm by NMR and mass spec (m/z=278).

Step 3



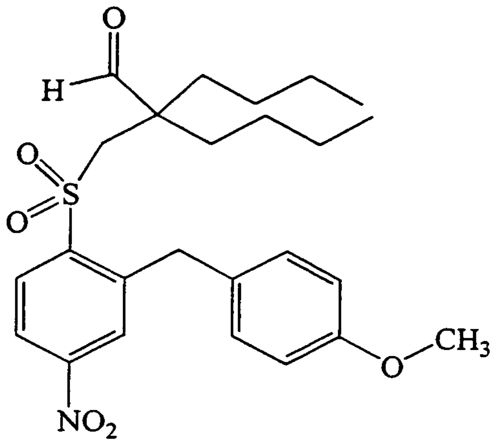
$C_{25}H_{33}NO_4S$ fw=443.61

Dissolve 10.12 gms (0.036 moles) of product 2 with 200 mls anhydrous DMSO. Place in a 500 ml round bottom flask with magnetic stir bar. Fit flask with water condenser, N_2 inlet, and stopper. Add 1.84 gms Li_2S (0.040 moles Aldrich 21,324-1). Place flask in oil bath and heat at 75°C under N_2 overnight then cool to room temperature.

Weigh out 10.59 gms dibutyl mesylate (0.040 moles). Dissolve with anhydrous DMSO and add to reaction solution. Purge well with N_2, heat overnight at 80°C.

Cool to room temperature. Prepare 500 mls of 5% acetic acid in a 2 liter beaker. While stirring, slowly add reaction mixture. Stir 30 min. Extract with ether 3 times. Combine organic layers and extract with water and sat'd NaCl. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry oil on vacuum line. Obtain pure product by column chromatography using 95% hexane and 5% ethyl acetate as the mobile phase. Dry wt=7.8 gms. Obtain NMR and mass spec (m/z=444).

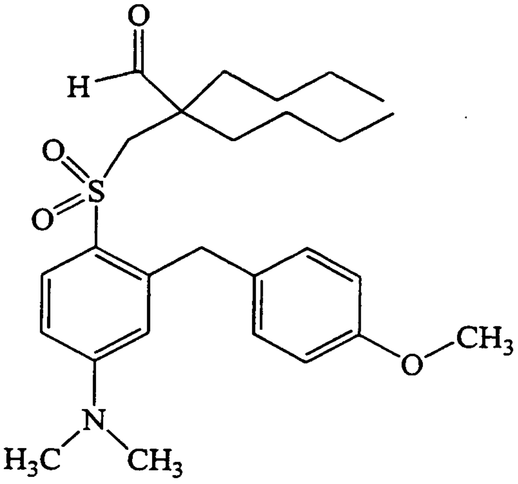
Step 4



$C_{25}H_{33}NO_6S$ fw=475.61

Dissolve 9.33 gms (0.021 moles) of product 3 with 120 mls anhydrous methylene chloride. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice bath under N_2 purge. Slowly add 11.54 gms 3-chloroperbenzoic acid (0.0435 moles, Fluka 25800, ~65%). After addition is complete warm to room temperature and monitor reaction by TLC. Reaction goes quickly to the sulphoxide intermediate but takes 8 hrs to convert to the sulphone. Chill solution over night in freezer. Filter solid from reaction, extract filtrate with 10% K_2CO_3. Extract aqueous layer twice with methylene choride. Combine organic layers and dry with $MgSO_4$. Filter and rotovap to dryness. Obtain pure product by crystallizing from ethanol or isolating by column chromatography. Obtain NMR and mass spec (m/z=476).

Step 5



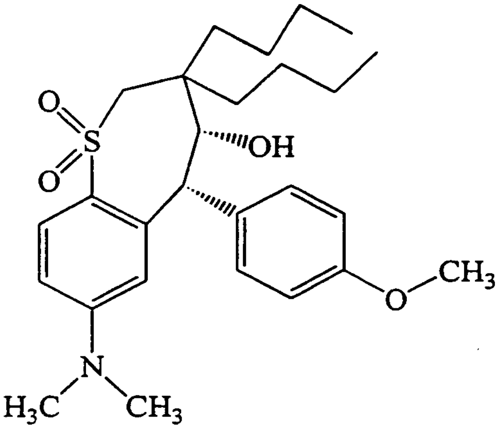
$C_{27}H_{39}NO_4S$ fw=473.68

Reaction is done in a 300 ml stainless steel Parr stirred mini reactor. Place 9.68 gms (0.0204 moles) of product 4 in reactor base. Add 160 mls ethanol. For safety reasons next two compounds are added in a N_2 atmosphere glove bag. In glove bag, add 15.3 mls formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich 20,569-9). Seal reactor before removing from glove bag. Purge reactor three times with H_2. Heat to 55°C under H_2. Run reaction at 200 psig H_2, 55°C, and a stir rate of 250 rpm. Run overnight under these conditions.

Cool reactor and vent H_2. Purge with N_2. Check progress of run by TLC. Reaction is a mixture of desired product and intermediate. Filter reaction mixture over a bed of celite washing well with ether. Rotovap and redissolve with ether. Extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line.

Charge reactor again with same amounts, seal reactor and run overnight under same conditions. After second run all of the material has been converted to the desired product. Cool and vent H_2 pressure. Purge with N_2. Filter over a bed of celite, washing well with ether. Rotovap to dryness. Dissolve with ether and extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line. Obtain NMR and mass spec (m/z=474).

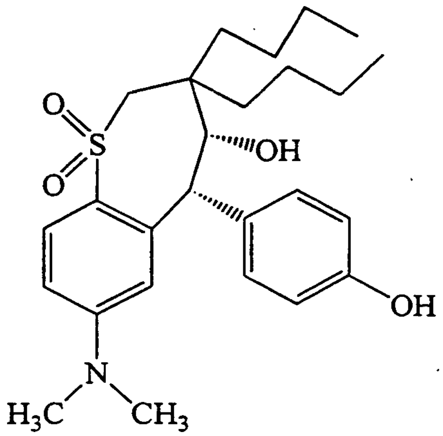
Step 6



$C_{27}H_{39}NO_4S$ fw=473.68

Dissolve 8.97 gms (0.0189 mole) of product 5 with 135 mls anhydrous THF. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice/salt bath under N_2 purge. Slowly add 2.55 gms potassium t-butoxide (0.227 mole Aldrich 15,667-1). After addition is complete, continue to stir at -10°C monitoring by TLC. Once reaction is complete, quench by adding 135 mls 10% HCl stirring 10 min. Extract three times with ether. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Crystallize from ether. Obtain NMR and mass spec (m/z=474).

Step 7

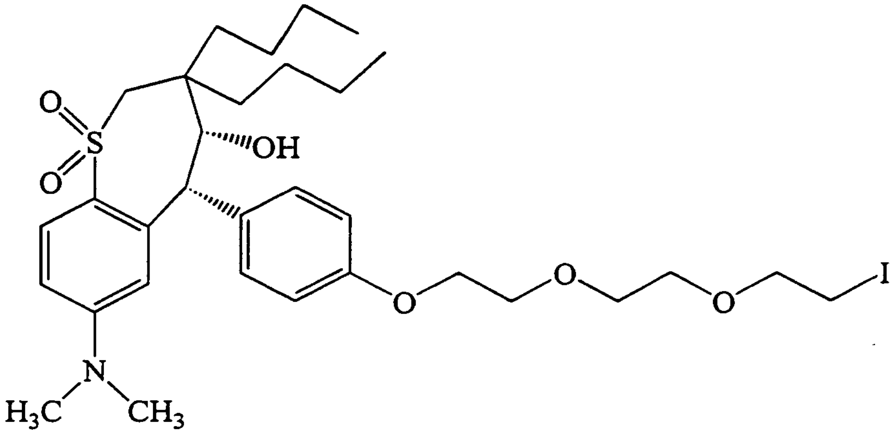


$C_{26}H_{37}NO_4S$ fw=459.65

Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N_2 purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

Chill solution with ice bath. Quench with 100 mls 10% K_2CO_3 while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl, once H_2O, and once with saturated NaCl solution. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec (m/z=460).

Step 8



$C_{32}H_{48}NO_6SI$ fw=701.71

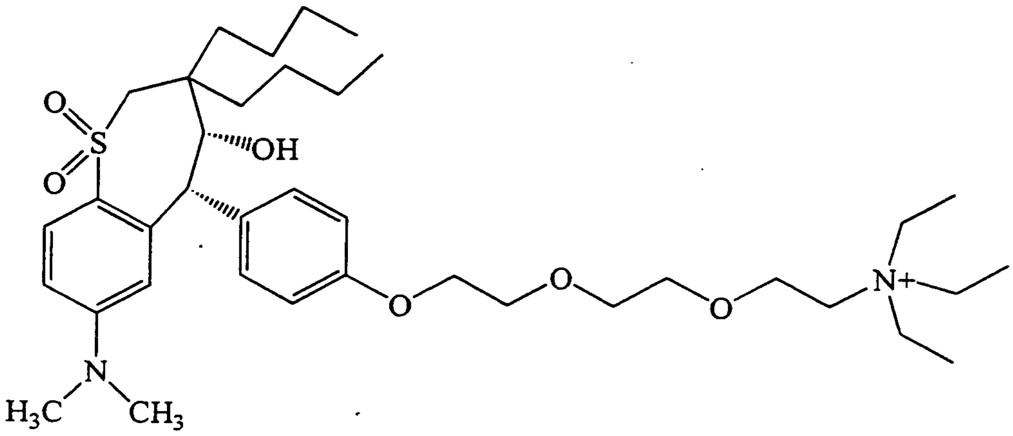
Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 60% disp. in mineral oil) in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill NaH with ice bath and begin N_2 purge.

Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 mls anhydrous DMF. Add to the cold NaH. Stir at cold temperature for 30 min. Add 1.33 gms K_2CO_3 (9.57 mmoles Fisher P-208).

Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane (43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous DMF. Add to cold reaction mixture. Warm to room temperature then heat to 40°C overnight under N_2.

Cleanup by diluting with ether and extracting sequentially with 5% NaOH, H_2O, and saturated NaCl. Dry organic layer with $MgSO_4$, filter and dry. Obtain pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and mass spec (m/z=702).

Step 9



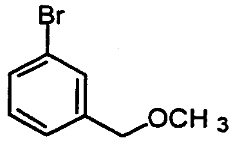
$C_{38}H_{63}N_2O_6SI$ fw=802.90

Dissolve 1.0 gms (1.43 mmoles) of product 8 with 10 mls anhydrous acetonitrile. Place in a 3 ounce Fischer-Porter pressure reaction vessel with magnetic stir bar. Add 2.9 gms triethyl amine (28.6 mmoles Aldrich 23,962-3) dissolved in 10 mls anhydrous acetonitrile. Purge well with N_2 then close system. Heat at 45°C. Monitor reaction by TLC. Reaction is usually complete in 48 hrs.

Perform cleanup by removing acetonitrile under vacuum. Redissolve with anhydrous chloroform and precipitate quaternary ammonium salt with ether. Repeat several times. Dry to obtain crystalline product. Obtain NMR and mass spec (m/z=675).

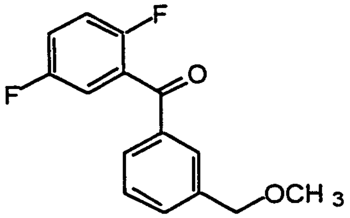
Example 1399

Step 1. Preparation of **1**



To a solution of 144 g of KOH (2560 mmol) in 1.1 L of DMSO was added 120 g of 2-bromobenzyl alcohol (641 mmol) slowly via addition funnel. Then was added 182 g of methyliodide (80 mL, 1282 mmol) via addition funnel. Stirred at ambient temperature for fifteen minutes. Poured reaction contents into 1.0 L of water and extracted three times with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purified by silica-gel chromatography through a 200 mL plug using hexanes (100%) as elutant yielded 103.2 g (80%) of **1** as a clear colorless liquid. ^{1}H NMR ($CDCl_3$) d 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, 2H), 7.12 (d, J = 7.45, 1H), 7.50 (s, 1H).

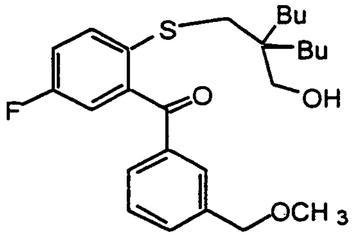
Step 2. Preparation of **2**



To a cooled (-78 °C) solution of 95 g (472 mmol) of **1** in 1.5 L THF was added 240 mL of 2.5 M n-butyl lithium (576 mmol). The mixture was stirred for one hour, and then to it was added 180 g of zinc iodide (566 mmol) dissolved in 500 ml THF. The mixture was stirred thirty minutes, allowed to warm to 5 C, cooled to -10 °C and to it was added 6 g of $Pd(PPh_3)_4$ (5.2 mmol) and 125 g 2,5-difluorobenzoyl chloride (708 mmol). The mixture was stirred at ambient temperature for 18 hoursand then cooled to 10 °C, quenched with water, partitioned between ethyl acetate and water, and washed organic layer with 1N HCL and with 1N NaOH. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography

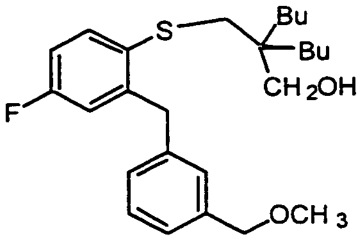
(Waters Prep-500) using 5% ethyl acetate/hexanes as elutant gave 53.6 g (43 %) of **2** as an orange oil. ^{1}H NMR ($CDCl_3$) d 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H).

Step 3. Preparation of **3**



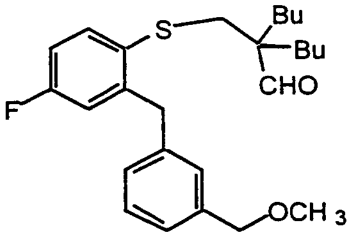
A solution of 53 g (202.3 mmol) of **2** and 11.2 g Li2S (242.8 mmol) in 250 mL DMF was heated to 100 °C for 18 hours. The reaction was cooled (0 °C) and 60.7 g of X' (the cyclic sulfate compound of example 1397) (242.8 mmol) in 50 mL DMF was added. Stirred at ambient temperature for 18 hours then condensed in vacuo. Added 1 L water to organic residue and extracted twice with diethyl ether. Aqueous layer acidified (pH 1) and refluxed 2 days. Cooled to ambient temperature and extracted with methylene chloride, dried organic layer over $MgSO_4$ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate / hexanes as elutant gave 42.9 g (48 %) of **3** as a yellow oil. ^{1}H NMR ($CDCl_3$) d 0.86 (t, J = 7.25 Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 (s, 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, J = 8.26 Hz and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and 2.82 Hz, 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, 2H), 7.69 (d, J = 7.85 Hz, 1H), 7.74 (s, 1H).

Step 4. Preparation of **4**



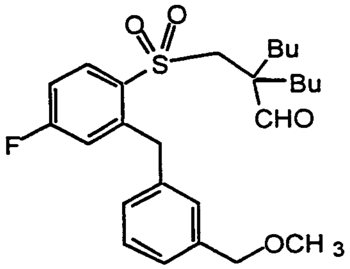
To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of **3** in 200 mL of methylene chloride was added 21.6 g trifluoromethane sulfonic acid (12.8 mL, 144 mmol) followed by the addition of 22.4 g triethyl silane (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, quenched with water and warmed to ambient temperature. Partitioned between methylene chloride and water, dried the organic layer over $MgSO_4$ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate/ hexanes as elutant gave 24.2 g (60%)of **4** as a oil. ^1H NMR ($CDCl_3$) d 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), 1.46 (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (s, 2H), 4.42 (s, 2H), 6.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 7.09 (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 - 7.32 (m, 2H), 7.42 (m, 1H).

Step 5. Preparation of **5**



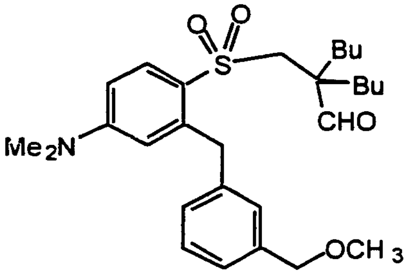
To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of **4** in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water and extracted three times with ethyl acetate. Washed organics with 5% HCl (300 mL) and then with brine (300 mL), dired organics over $MgSO_4$ and condensed in vacuo to give 23.1 g (96 %) of **5** as a light brown oil. ^1H NMR ($CDCl_3$) d 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, J = 9.66 Hz and 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, J = 7.46 Hz, 1H), 7.14 (s, 1H), 7.19 (d, J = 7.65 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

Step 6. Preparation of **6**



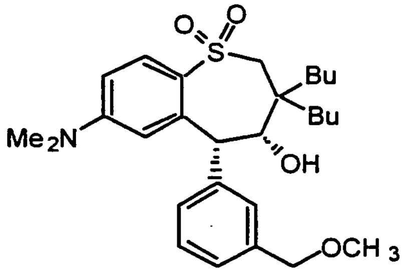
To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of **5** in 200 mL methylene chloride was added 28.6 g meta cholorperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na_2SO_3, partitioned between water and methylene chloride. Dried organic layer over $MgSO_4$ and condensed in vacuo to give 24.5 g (98%) of **6** as a light yellow oil. ^1H NMR ($CDCl_3$) d 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (s, 2H), 3.39 (s, 3H), 4.44 (s, 2H), 4.50 (s, 2H), 6.93 (d, J = 9.07 Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (s, 1H), 9.38 (s, 1H).

Step 7. Preparartion of **7**



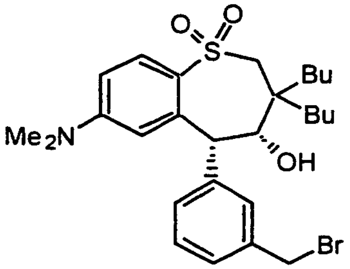
To a solution of 24.5 g (52.9 mmol) of **6** in 20 mL of THF contained in a stainless steel reaction vessel was added 100 mL of a 2.0 M solution of dimethyl amine and 20 mL of neat dimethyl amine. The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 15 % ethyl acetate/hexanes gave 21.8 g (84 %) of **7** as a clear colorless oil. ^{1}H NMR ($CDCl_3$) d 0.85 (t, J = 7.25 Hz, 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 - 1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, 2H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (s, 1H), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 1H), 9.36 (s, 1H).

Step 8. Preparation of **8**



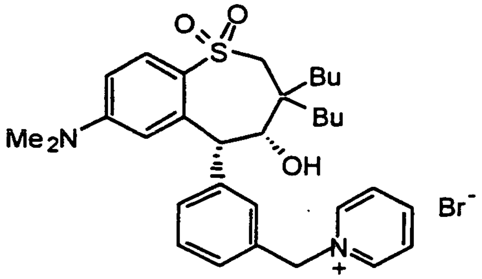
A solution of 21.8 g (44.8 mmol) of **7** in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirred for 30 minutes, then quenched with 50 mL of saturated ammonium chloride. The organic layer was partitioned between ethyl acetate and water, dried over MgSO4 and concentrated in vacuo. Purification by recrystalization from ~10% ethyl acetate/hexanes gave 15.1 g of **8** as a white solid. The mother liquor was purified by silica gel chromatography (Waters Prep-500) using 30% ethyl acetate/hexanes as the elutant to give 3.0 g of **8** as a white solid. MS (FABLi$^+$) m/e 494.6. HRMS (EI$^+$) calculated for M+H 487.2756. Found 487.2746.

Step 9. Preparation of **9**



A solution of 2.0 g (4.1 mmol) of **8** in 20 mL of methylene chloride was cooled to -60 °C. 4.1 mL of a 1M solution of boron tribromide was added. Stirred at ambient temperature for thirty minutes. Cooled reaction to ~10 °C and quenched with 50 mL of water. The organic layer was partitioned between methylene chloride and water, dried over $MgSO_4$ and concentrated in vacuo. Purification by recrystalization from 50% ethyl acetate/methylene chloride gave 1.95 g (89%) of **9** as a white solid. MS (FABH$^+$) m/e 537. HRMS (FAB) calculated for M 536.1834. Found 536.1822.

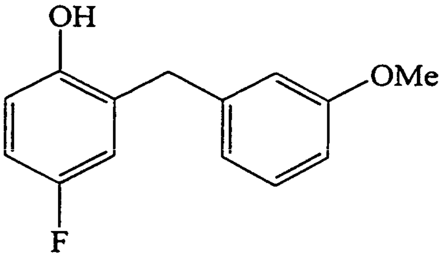
Step 10. Preparation of **10**



A solution of 1.09 g (2.0 mmol) of **9** and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacuo. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of **10** as an off white solid. MS (FAB^+) m/e 535.5.

Example 1400

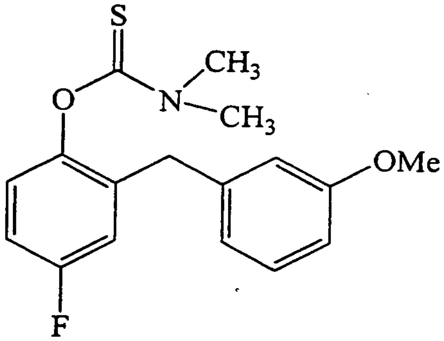
Step 1



$C_{14}H_{13}O_2F$ fw=232.25

A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N_2 gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N_2. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H_2O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aq. KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ^1H NMR and MS [$(M + H)^+ = 233$] confirmed desired structure.

Step 2

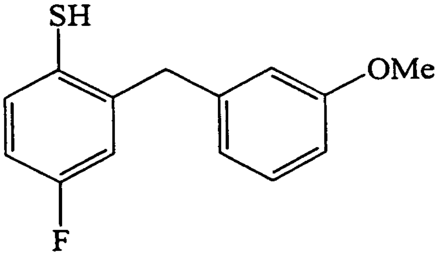


$C_{17}H_{18}NO_2FS$ fw=319.39

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenol

(455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ^1H NMR and MS [$(M+H)^+$ = 320] confirm desired structure.

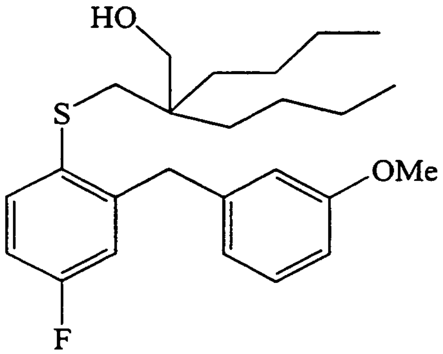
Step 3



$C_{14}H_{13}OFS$ fw=248.32

A 12-liter, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temparature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temparature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H_2O. The aqueous extracts were combined, acidified with concentrated HCl, and extracted with ethyl ether. The ether extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ^1H NMR confirmed desired structure.

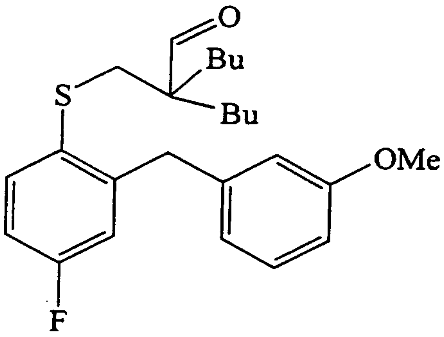
Step 4



$C_{25}H_{35}O_2FS$ fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temparature, 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H_2O. The aqueous solution was washed with ethyl ether, and concentrated H_2SO_4 was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried ($MgSO_4$), filtered, and conc'd *in vacuo* to give an amber oil (143.94g/85% yield). ^1H NMR and MS [$(M + H)^+ = 419$] confirm the desired structure.

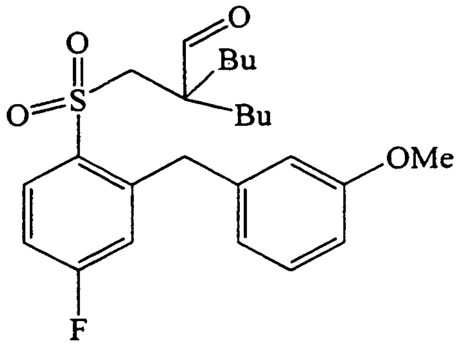
Step 5



$C_{25}H_{33}O_2FS$ fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2. The corresponding alcohol (143.94g/343.8mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS [$(M + H)^+ = 417$] confirm the desired structure.

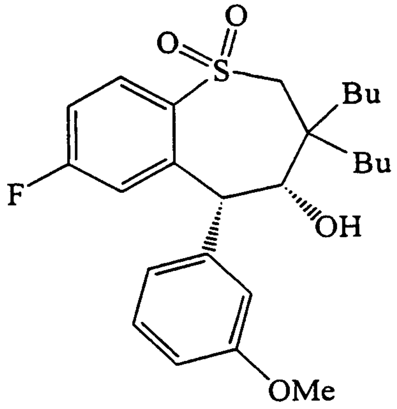
Step 6



$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. The corresponding sulfide (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K_2CO_3. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ^1H NMR confirmed the desired structure.

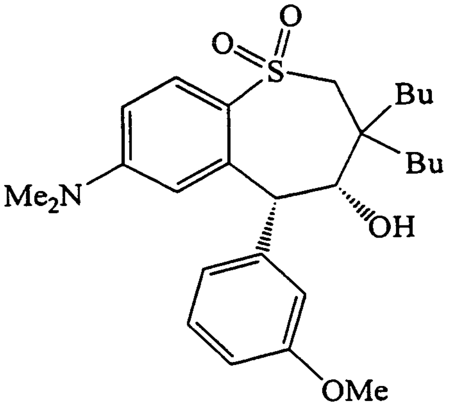
Step 7



$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 C. Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by recryst. from 80/20 hexane/ethyl acetate to give a white solid (32.18 g). The mother liquor was concentrated in vacuo and recrystelized from 95/5 toluene/ethyl acetate to give a white solid (33.60g/ combined yield: 71%). ^1H NMR confirmed the desired product.

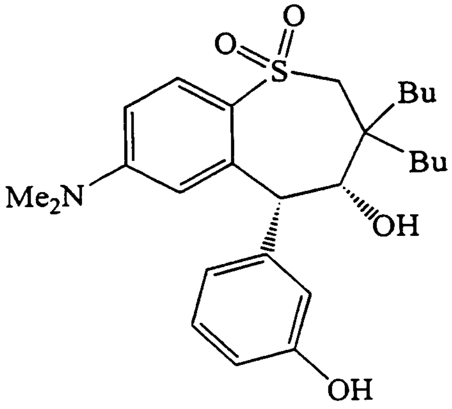
Step 8



$C_{27}H_{39}O_4NS$ fw=473.67

A Fisher porter bottle was fitted with N_2 line and magnetic stirrer. The system was purged with N_2. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a CO_2/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H_2O, saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a white solid (28.5g/96% yield). ^1H NMR confirmed the desired structure.

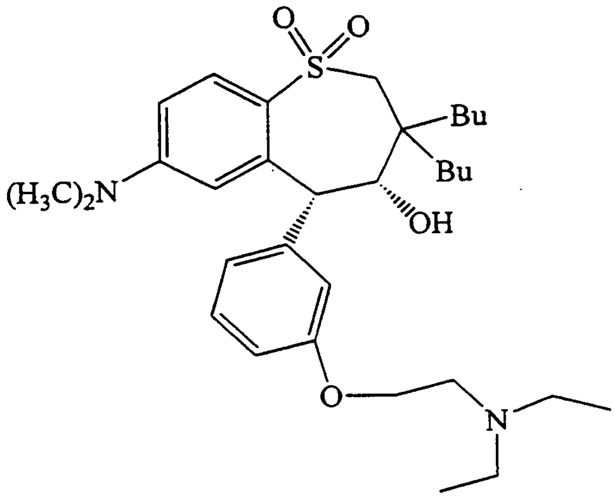
Step 9



$C_{26}H_{37}O_4NS$ fw=459.64

A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2. The corresponding methoxy-compound (6.62g/14.0mmol) and $CHCl_3$ (150 mL) were added. The reaction mixture was cooled to -78 C, and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature After 4 h, the reaction mixture was cooled to 0 C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The $CHCl_3$ and ether extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

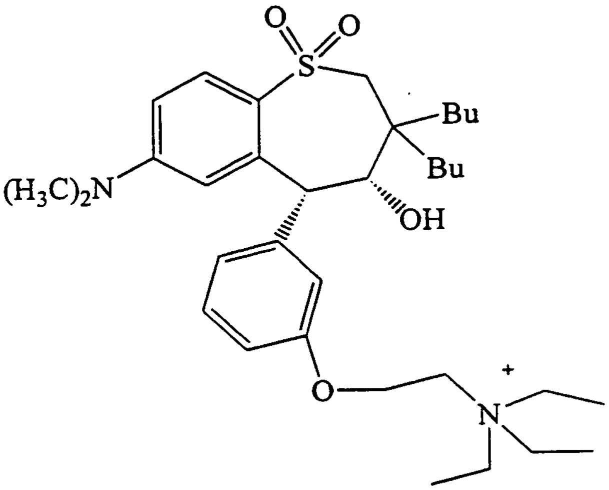
Step 10



In a 250 ml single neck round bottom Flask with stir bar place 2- diethylamineoethyl chloride hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 mmol,4.12g), 34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg , 2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product(previous step) 1.1 g (2.4 mmilomoles in 5 ml DMF and the ether solution prepared above. Heat to 40C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms).The product may be further purified by chromatography (SiO2 99% ethyl acetate/1% NH4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec , and H1 NMR)

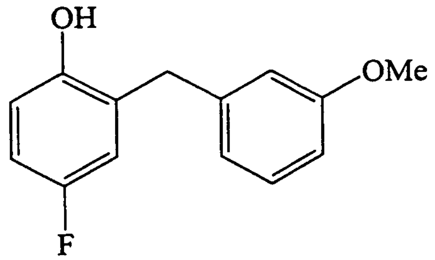
Step 11



The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was placed in 5 ml acetonitrile in a fischer-porter bottle and heated to 45 C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9 , H NMR).

Example 1401

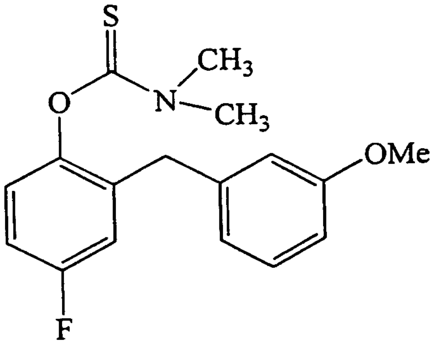
Step 1



$C_{14}H_{13}O_2F$ fw=232.25

A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N_2 gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N_2. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H_2O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aqueous KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ^1H NMR and MS $[(M + H)^+ = 233]$ confirmed desired structure.

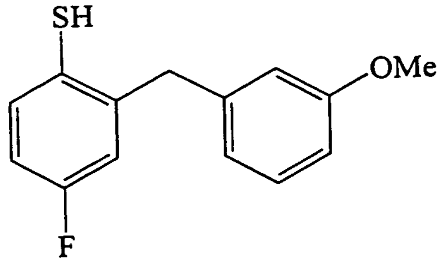
Step 2



$C_{17}H_{18}NO_2FS$ fw=319.39

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ^1H NMR and MS $[(M+H)^+ = 320]$ confirm desired structure.

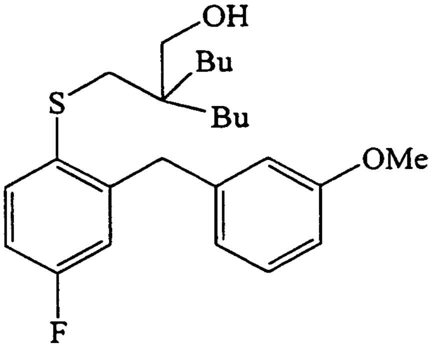
Step 3



$C_{14}H_{13}OFS$ fw=248.32

A 12-liter, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H_2O. The aqueous extracts were combined, acidified with conc. HCl, and extracted with ethyl ether. The ether extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ^1H NMR confirmed desired structure.

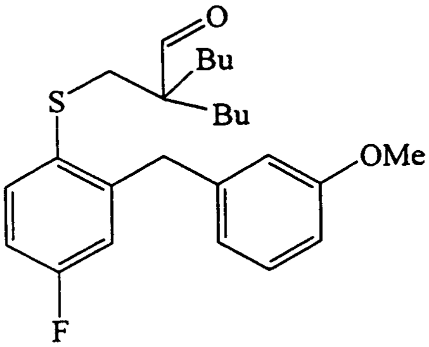
Step 4



$C_{25}H_{35}O_2FS$ fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H_2O. The aqueous solution was washed with ethyl ether, and conc. H_2SO_4 was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an amber oil (143.94g/85% yield). ^{1}H NMR and MS [$(M + H)^+ = 419$] confirm the desired structure.

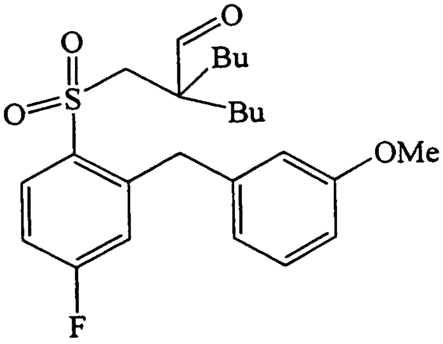
Step 5



$C_{25}H_{33}O_2FS$ fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2. The corresponding alcohol (143.94 g/343.8 mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS [$(M + H)^+ = 417$] confirm the desired structure.

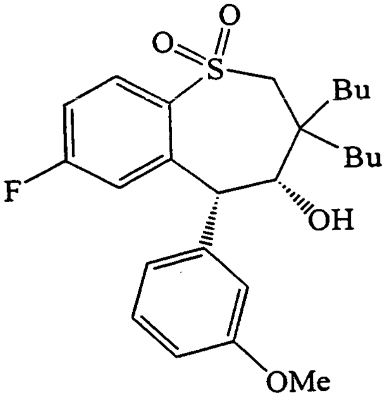
Step 6



$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. The corresponding sulfide (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K_2CO_3. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ^1H NMR confirmed the desired structure.

Step 7

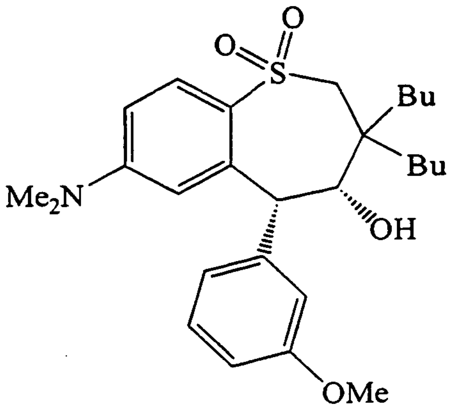


$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 C.

Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by recrystallized from 80/20 hexane/ethyl acetate to give a white solid (32.18g). The mother liquor was concentrated in vacuo and recrystallized from 95/5 toluene/ethyl acetate to give a white solid (33.60g, combined yield: 71%). ^1H NMR confirmed the desired product.

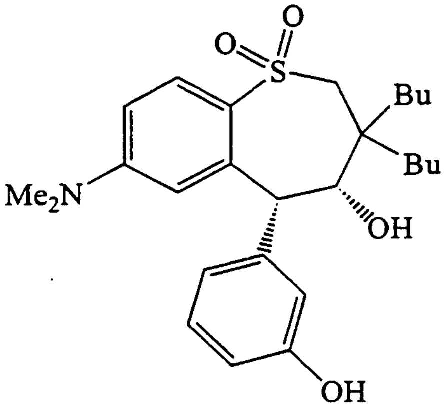
Step 8



$C_{27}H_{39}O_4NS$ fw=473.67

A Fisher porter bottle was fitted with N_2 line and magnetic stirrer. The system was purged with N_2. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a CO_2/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H_2O, saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a white solid (28.5g/96% yield). ^1H NMR confirmed the desired structure.

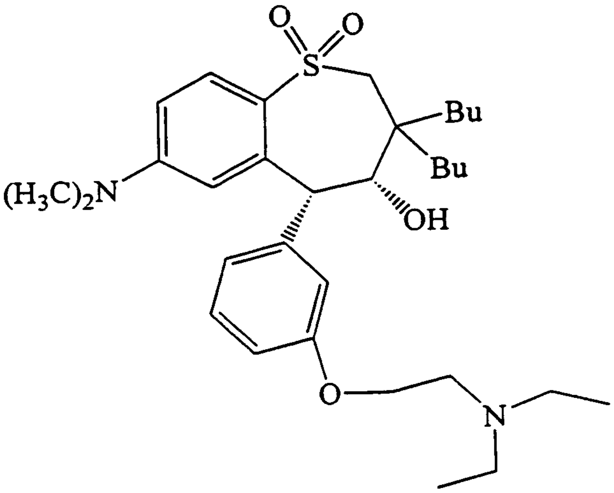
Step 9



$C_{26}H_{37}O_4NS$ fw=459.64

A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2. The corresponding methoxy-compound (6.62g/14.0mmol) and $CHCl_3$ (150 mL) were added. The reaction mixture was cooled to -78 C, and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature After 4 h, the reaction mixture was cooled to 0 C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The $CHCl_3$ and ether extracts were combined, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

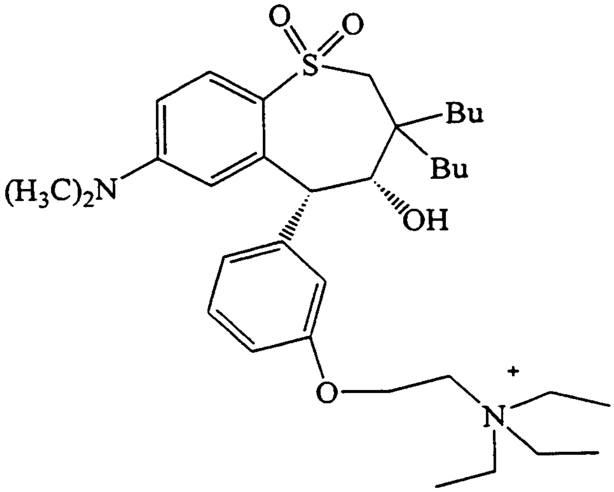
Step 10



In a 250 ml single neck round bottom flask with stir bar place 2- diethylamineoethyl chloride hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N KOH (aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

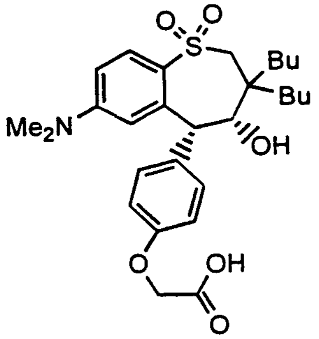
In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product (previous step) 1.1 g (2.4 mmol in 5 ml DMF and the ether solution prepared above. Heat to 40C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over Magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (silica 99% ethyl acetate/1% NH4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec , and H1 NMR)

Step 11



The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and iodoethane (1.6 gms (10.02 mmilimoles)was place in 5 ml acetonitrile in a Fischer-Porter bottle and heated to 45 C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9, ^1H NMR).

Example 1402



(4R-cis)-5-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]thio]-1H-tetrazole-1-acetic acid

Step 1. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol

To a stirred solution of 23.66 g of 95% sodium hydride (0.94 mol) in 600 mL of dry toluene was added 100.0 g of 4-fluorophenol (0.89 mol) at 0°C. The mixture was stirred at 90°C for 1 hour until gas evolution stopped. The mixture was cooled down to room temperature and a solution of 139.71 g of 3-methoxybenzyl chloride (0.89 mol) in 400 mL of dry toluene was added. After refluxing for 24 hours, the mixture was cooled to room temperature and quenched with 500 mL of water. The organic layer was separated, dried over $MgSO_4$, and concentrated under high vacuum. The remaining starting materials were removed by distillation. The crude dark red oil was filtered through a layer of 1 L of silica gel with neat hexane to yield 53.00 g (25.6%) of the product as a pink solid: ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.90 (s, 2H), 4.58 (s, 1H), 6.70-6.74 (m, 1H), 6.79-6.88 (m, 4H), 7.11-7.16 (m, 2H).

Step 2. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

Step 2a. Preparation of thiocarbamate

To a stirred solution of 50.00 g (215.30 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol in 500 mL of dry DMF was added 11.20 g of 60% sodium hydride dispersion in mineral oil (279.90 mmol) at 2°C. The mixture was allowed to warm to room temperature and 26.61 g of dimethylthiocarbamoyl chloride (215.30 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with 100 mL of water in an ice bath. The solution was extracted with 500 mL of diethyl ether. The ether solution was washed with 500 mL of water and 500 mL of brine. The ether solution was dried over $MgSO_4$ and stripped to dryness. The crude product was filtered through a plug of 500 mL silica gel using 5% ethyl acetate/hexane to yield 48.00 g (69.8%) of the product as a pale white solid: ^1H NMR ($CDCl_3$) δ 3.21 (s, 3H), 3.46 (s, 3H), 3.80 (s, 3H), 3.82 (s, 2H), 6.78-6.86 (m, 3H), 6.90-7.00 (m, 2H), 7.09 (d, J = 8.7 Hz, 2H).

Step 2b. Rearrangement and hydrolysis of thiocarbamate to 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

A stirred solution of 48.00 g (150.29 mmol) of thiocarbamate (obtained from Step 2a) in 200 mL of diphenyl ether was refluxed at 270°C overnight. The solution was cooled down to room temperature and filtered through 1 L of silica gel with 2 L of hexane to remove phenyl ether. The rearrangement product was washed with 5% ethyl acetate/hexane to give 46.00 g (95.8%) of the product as a pale yellow solid: ^1H NMR ($CDCl_3$) δ 3.02 (s, 3H), 3.10 (s, 3H), 3.80 (s, 3H), 4.07 (s, 2H), 6.82-6.86 (m, 3H), 6.93 (dt, J = 8.4 Hz, 2.7

Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.49 (dd, J = 6.0 Hz, 8.7 Hz, 1H).

To a solution of 46.00 g (144.02 mmol) of the rearrangement product (above) in 200 mL of methanol and 200 mL of THF was added 17.28 g of NaOH (432.06 mmol). The mixture was refluxed under nitrogen overnight. The solvents were evaporated off and 200 mL of water was added. The aqueous solution was washed with 200 mL of diethyl ether twice and placed in an ice bath. The aqueous mixture was acidified to pH 6 with concentrated HCl solution. The solution was extracted with 300 mL of diethyl ether twice. The ether layers were combined, dried over $MgSO_4$ and stripped to dryness to afford 27.00 g (75.5%) of the product as a brown oil: ^1H NMR ($CDCl_3$) δ 3.24 (s, 1H), 3.80 (s, 3H), 3.99 (s, 2H), 6.81-6.87 (m, 4H), 7.09 (d, J = 8.7 Hz, 2H), 7.27-7.33 (m, 1H).

Step 3. Preparation of dibutyl cyclic sulfate

Step 3a. Preparation of 2,2-dibutyl-1,3-propanediol.

To a stirred solution of di-butyl-diethylmalonate (Aldrich) (150g, 0.55 mol in dry THF (700ml) in an acetone/dry ice bath was added LAH (1 M THF) 662 ml (1.2 eq., 0.66 mol) dropwise maintaining the temperature between -20 to 0°C. The reaction was stirred at RT overnight. The reaction was cooled to -20°C and 40 ml of water, and 80 mL of 10% NaOH and 80 ml of water were added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated *in vacuo* to give diol 98.4 g (yield 95%) as an oil. MS spectra and proton and carbon NMR spectra were consistent with the product.

Step 3b. Preparation of dibutyl cyclic sulfite

A solution of 2,2-dibutyl-1,3-propanediol (103 g, 0.548 mol, obtained from Step 3a) and triethylamine

(221 g, 2.19 mol) in anhydrous methylene chloride (500 ml) was stirred at 0°C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise and within 5 min the solution turned yellow and then black when the addition was completed within half an hour. The reaction mixture was stirred for 3 hrs. at 0°C. GC showed that there was no starting material left. The mixture was washed with ice water twice then with brine twice. The organic phase was dried over magnesium sulfate and concentrated under vacuum to give 128 g (100%) of the dibutyl cyclic sulfite as a black oil. Mass spectrum (MS) was consistent with the product.

Step 3c. Oxidation of dibutyl cyclic sulfite to dibutyl cyclic sulfate

To a solution of the dibutyl cyclic sulfite (127.5 g , 0.54 mol, obtained from Step 3b) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium (III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. GC showed that there was no starting material left. The mixture was extracted with 300 ml of ether and the ether extract was washed three times with brine. The organic phase was dried over magnesium sulfate and passed through celite. The filtrate was concentrated under vacuum and to give 133 g (97.8%) of the dibutyl cyclic sulfate as an oil. Proton and carbon NMR and MS were consistent with the product.

Step 4. Preparation of aryl-3-hydroxypropylsulfide

To a stirred solution of 27.00 g (108.73 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)thiophenol (obtained from Step 2) in 270 mL of diglyme was added 4.35 g of 60% sodium hydride dispersion in mineral oil

(108.73 mmol) at 0°C. After gas evolution ceased, 29.94 g (119.60 mmol) of the dibutyl cyclic sulfate (obtained from Step 3c) was added at 0°C and stirred for 10 minutes. The mixture was allowed to warm up to room temperature and stirred overnight. The solvent was evaporated and 200 mL of water was added. The solution was washed with 200 mL of diethyl ether and added 25 mL of concentrated sulfuric acid to make a 2.0 M solution that was refluxed overnight. The solution was extracted with ethyl acetate and the organic solution was dried over $MgSO_4$ and concentrated in vacuo. The crude aryl-3-hydroxypropylsulfide was purified by silica gel chromatography (Waters Prep 500) using 8% ethyl acetate/hexane to yield 33.00 g (72.5%) of the product as a light brown oil: ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.1 Hz, 6H), 1.14-1.34 (m, 12H), 2.82 (s, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10 (s, 2H), 6.77-6.92 (m, 4H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.41 (dd, *J* = 8.7 Hz, 5.7 Hz, 1H).

Step 5. Preparation of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

To a stirred solution of 20.00 g (47.78 mmol) of aryl-3-hydroxypropylsulfide (obtained from Step 4) in 1 L of methylene chloride was added 31.50 g of 96% (1*R*)-(-)-(8,8-dichloro-10-camphor-sulfonyl)oxaziridine (100.34 mmol, Aldrich) at 2°C. After all the oxaziridine dissolved the mixture was placed into a -30°C freezer for 72 hours. The solvent was evaporated and the crude solid was washed with 1 L of hexane. The white solid was filtered off and the hexane solution was concentrated in vacuo. The crude oil was purified on a silica gel column (Waters Prep 500) using 15% ethyl acetate/hexane to afford 19.00 g (95%) of the enantiomerically-enriched aryl-3-hydroxypropylsulfoxide as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.82-0.98 (m, 6H), 1.16-1.32 (m, 12H), 2.29 (d, J = 13.8 Hz, 1H), 2.77 (d, J = 13.5 Hz, 1H), 3.45 (d, J = 12.3 Hz, 1H), 3.69 (d, J = 12.3 Hz, 1H), 3.79 (s, 3H), 4.02 (q, J = 15.6 Hz, 1H), 6.83-6.93 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 7.18-7.23 (m, 1H), 7.99-8.04 (m, 1H). Enantiomeric excess was determined by chiral HPLC on a (*R,R*)-Whelk-O column using 5% ethanol/hexane as the eluent. It showed to be 78% e.e. with the first eluting peak as the major product.

Step 6. Preparation of enantiomerically-enriched aryl-3-propanalsulfoxide

To a stirred solution of 13.27 g of triethylamine (131.16 mmol, Aldrich) in 200 mL dimethyl sulfoxide were added 19.00 g (43.72 mmol) of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide (obtained from Step 5) and 20.96 g of sulfur trioxide-pyridine (131.16 mmol, Aldrich) at room temperature. After the mixture was stirred at room temperature for 48 hours, 500 mL of water was added to the mixture and stirred vigorously. The mixture was then extracted with 500 mL of ethyl acetate twice. The ethyl acetate layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude oil was filtered through 500 mL of silica gel using 15% ethyl acetate/hexane to give 17.30 g (91%) of the enantiomerically-enriched aryl-3-propanalsulfoxide as a light orange oil: ^{1}H NMR ($CDCl_3$) δ 0.85-0.95 (m, 6H), 1.11-1.17 (m, 4H), 1.21-1.39 (m, 4H), 1.59-1.76 (m, 4H), 1.89-1.99 (m, 1H), 2.57 (d, J = 14.1 Hz, 1H), 2.91 (d, J = 13.8 Hz, 1H), 3.79 (s, 3H), 3.97 (d, J = 15.9 Hz, 1H), 4,12 (d, J = 15.9 Hz, 1H), 6.84-6.89 (m, 3H), 7.03 (d, J = 8.4 Hz, 2H), 7.19 (dt, J = 8.4 Hz, 2.4 Hz, 1H), 8.02 (dd, J = 8.7 Hz, 5.7 Hz, 1H), 9.49 (s, 1H).

Step 7. Preparation of the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R)

To a stirred solution of 17.30 g (39.99 mmol) of enantiomerically-enriched aryl-3-propanalsulfoxide (obtained from Step 6) in 300 mL of dry THF at -15°C was added 48 mL of 1.0 M potassium *t*-butoxide in THF (1.2 equivalents) under nitrogen. The solution was stirred at -15°C for 4 hours. The solution was then quenched with 100 mL of water and neutralized with 4 mL of concentrated HCl solution at 0°C. The THF layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R) was purified by silica gel chromatography (Waters Prep 500) using 15% ethyl acetate/hexane to give 13.44 g (77.7%) of the product as a white solid: ^1H NMR ($CDCl_3$) δ 0.87-0.97 (m, 6H), 1.16-1.32 (m, 4H), 1.34-1.48 (m, 4H), 1.50-1.69 (m, 4H), 1.86-1.96 (m, 1H), 2.88 (d, J = 13.0 Hz, 1H), 3.00 (d, J = 13.0 Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), 4.48 (s, 1H), 6.52 (dd, J = 9.9 Hz, 2.4 Hz, 1H), 6.94 (d, J = 9 Hz, 2H), 7.13 (dt, J = 8.4 Hz, 2.4 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.82 (dd, J = 8.7 Hz, 5.7 Hz, 1H).

Step 8. Preparation of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a stirred solution of 13.44 g (31.07 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (obtained from Step 7) in 150 mL of methylene chloride was added 9.46 g of 68% *m*-chloroperoxybenzoic acid (37.28 mmol, Sigma) at 0 °C. After stirring at 0 °C for 2 hours, the mixture was allowed to warm up to room temperature and stirred for 4 hours. 50 mL of saturated Na_2SO_3 was added into the mixture and stirred for 30 minutes. The solution was then neutralized with

50 mL of saturated $NaHCO_3$ solution. The methylene chloride layer was separated, dried over $MgSO_4$, and concentrated in vacuo to give 13.00 g (97.5%) of the enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a light yellow solid: ^1H NMR ($CDCl_3$) δ 0.89-0.95 (m, 6H), 1.09-1.42 (m, 12H), 2.16-2.26 (m, 1H), 3.14 (q, J = 15.6 Hz, 1H), 3.87 (s, 3H), 4.18 (s, 1H), 5.48 (s, 1H), 6.54 (dd, J = 10.2 Hz, 2.4 Hz, 1H), 6.96-7.07 (m, 3H), 7.40 (d, J = 8.1 Hz, 2H), 8.11 (dd, J = 8.6 Hz, 5.9 Hz, 1H).

Step 9. Preparation of enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a solution of 13.00 g (28.98 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 8) in 73 mL of dimethylamine (2.0 M in THF, 146 mmol) in a Parr Reactor was added about 20 mL of neat dimethylamine. The mixture was sealed and stirred at 110°C overnight, and cooled to ambient temperature. The excess dimethylamine was evaporated. The crude oil was dissolved in 200 mL of ethyl acetate and washed with 100 mL of water, dried over $MgSO_4$ and concentrated in vacuo. Purification on a silica gel column (Waters Prep 500) using 20% ethyl acetate/hexane gave 12.43 g (90.5%) of the enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a colorless solid: ^1H NMR ($CDCl_3$) δ 0.87-0.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), 2.81 (s, 6H), 2.99 (d, J = 15.3 Hz, 1H), 3.15 (d, J = 15.3 Hz, 1H), 3.84 (s, 3H), 4.11 (d, J = 7.5 Hz, 1H), 5.49 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.42 (d,

J = 8.4 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). The product was determined to have 78% e.e. by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. Recrystallization of this solid from ethyl acetate/hexane gave 1.70 g of the racemic product. The remaining solution was concentrated and recrystallized to give 9.8 g of colorless solid. Enantiomeric excess of this solid was determined by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. It showed to have 96% e.e with the first eluting peak as the major product.

Step 10: Demethylation of 5-(4′-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a solution of 47 g (99 mmol) of enantiomeric-enriched (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 9) in 500 mL of methylene chloride at -10 °C was added dropwise a solution of boron tribromide (297 mL, 1M in methylene chloride, 297 mmol), and the resulting solution was stirred cold (-5 °C to 0 °C) for 1 hour or until the reaction was complete. The reaction was cooled in an acetone-dry ice bath at -10 °C, and slowly quenched with 300 mL of water. The mixture was warmed to 10 °C, and further diluted with 300 mL of saturated sodium bicarbonate solution to neutralize the mixture. The aqueous layer was separated and extracted with 300 mL of methylene chloride, and the combined extracts were washed with 200 mL of water, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in 500 mL of ethyl acetate and stirred with 50 mL of glacial acetic acid for 30 minutes at ambient temperature. The mixture was washed twice with 200 mL of water, 200 mL of brine, dried over $MgSO_4$ and concentrated in vacuo to give the crude 4-hydroxyphenyl intermediate. The solid residue was recrystallized from methylene chloride to give 37.5 g (82%) of the desired 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.84-0.97 (m, 6H), 1.1-1.5 (m, 10H), 1.57-1.72 (m, 1H), 2.14-2.28 (m, 1H), 2.83 (s, 6H), 3.00 (d, J = 15.3 Hz, 1H), 3.16 (d, J = 15.3 Hz, 1H), 4.11 (s, 2H), 5.48 (s, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 9, 2.4 Hz, 1H), 6.88 (d, 8,7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 9 Hz, 2H).

Alternatively, enantiomeric-enriched 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the intermediate just described, can be prepared via non-enantioselective synthesis followed by chiral chromatography separation. Oxidation of aryl-3-hydroxypropylsulfide (obtained from Step 4) with m-chloroperbenzoic acid (under the similar conditions as in Step 8, but with 2.2 equivalent of m-CPBA) gave the racemic sulfone intermediate. The sulfone was carried through the synthetic sequences (under the same conditions as in Step 7 and Step 9) to give the racemic 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide. The two enantiomers were further separated into the desired enantiomeric-enriched 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide by appropriate chiral chromatographic purification.

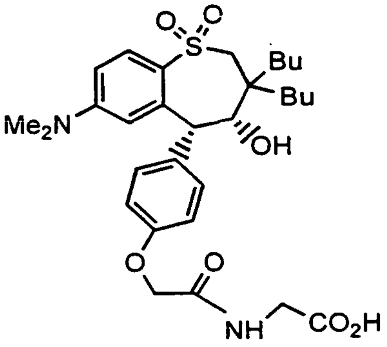
Step 11: Preparation of ester intermediate

To a solution of 1.0 g (2.18 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 10) in 10 mL dimethylformamide was added 60 mg (2.38 mmol) of 95% sodium hydride and stirred for 15 minutes. To the reaction mixture was added 400 µL (2.52 mmol) of benzyl 2-bromoacetate and stirred for two hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 1.30g (98%) of the ester intermediate: ^{1}H NMR ($CDCl_3$) δ 0.88-0.94 (m, 6H), 1.13-1.46 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.24 (m, 1H), 2.81 (s, 6H), 3.00 (d, J = 15.1 Hz, 1H), 3.16 (t, J = 15.1 Hz, 1H), 4.11 (s, 1H), 5.26 (s, 2H), 5.49 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 7.37 (s, 5H), 7.42 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H).

Step 12: Preparation of acid

A solution of 1.30 g (2.14 mmol) of ester intermediate (obtained from Step 1) in 40 mL ethanol with 10% palladium on carbon was placed under an atmosphere of hydrogen gas (40 psi) for three hours. The reaction mixture was filtered through celite and the solvent was evaporated to afford the desired title compound as a white solid: mp 119 - 123 °C; ^{1}H NMR ($CDCl_3$) δ 0.89-0.94 (m, 6H), 1.19-1.43 (m, 10H), 1.61-1.65 (m, 1H), 2.17-2.21 (m, 1H), 2.85 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (t, J = 14.9 Hz, 1H), 4.12 (s, 1H), 4.72 (s, 2H), 5.51 (s, 1H), 6.17 (s, 1H), 6.74 (d, J = 9.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for $C_{28}H_{40}NO_6S$: 518.2576. Found: 518.2599.

Example 1403



(4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

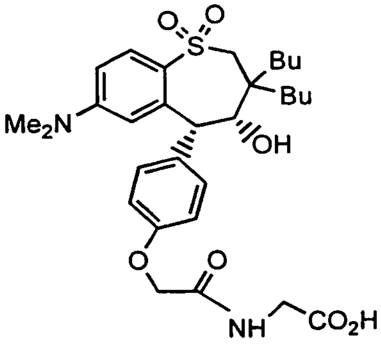
Step 1: Preparation of glycine ester intermediate

To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR ($CDCl_3$) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q, J_{AB} = 15.3 Hz, J = 48.9 Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, J = 7.0 Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 8.5 Hz, 2H), 7.17 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H).

Step 2: Preparation of acid

A solution of 7.3 g (12.1 mmol) of glycine ester intermediate (obtained from Step 1) and 1.5 g LiOH.H_2O (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45 °C for 2 hours. This was then cooled to ambient temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by recrystallization from ethyl acetate gave 5.45 g (78%) of the desired title compound as a white crystalline solid: mp 149-150 °C; ^1H NMR (CD_3OD) δ 0.88-0.98 (m, 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 (m, 1H), 2.79 (s, 6H), 3.11 (AB_q, J_{AB} = 15.3 Hz, J = 21.6 Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H), 5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS(ES+) Calc'd for $C_{30}H_{42}N_2O_7S$: 575.2712. Found: 575.2790. Anal. Calc'd for: $C_{30}H_{42}N_2O_7S$ C, 62.69; H, 7.37; N, 4.87. Found: C, 62.87; H, 7.56; N, 4.87.

Example 1403



(4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

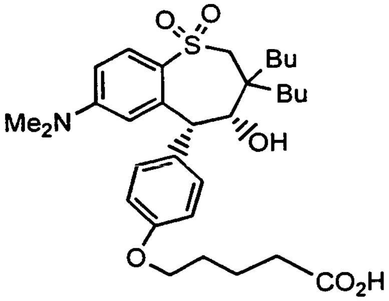
Step 1: Preparation of glycine ester intermediate

To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR ($CDCl_3$) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q, J_{AB} = 15.3 Hz, J = 48.9 Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, J = 7.0 Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 8.5 Hz, 2H), 7.17 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H).

Step 2: Preparation of acid

A solution of 7.3 g (12.1 mmol) of glycine ester intermediate (obtained from Step 1) and 1.5 g $LiOH.H_2O$ (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45 °C for 2 hours. This was then cooled to ambient temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by recrystallization from ethyl acetate gave 5.45 g (78%) of the desired title compound as a white crystalline solid: mp 149-150 °C; ^{1}H NMR (CD_3OD) δ 0.88-0.98 (m, 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 (m, 1H), 2.79 (s, 6H), 3.11 (AB_q, J_{AB} = 15.3 Hz, J = 21.6 Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H), 5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS(ES+) Calc'd for $C_{30}H_{42}N_2O_7S$: 575.2712. Found: 575.2790. Anal. Calc'd for: $C_{30}H_{42}N_2O_7S$ C, 62.69; H, 7.37; N, 4.87. Found: C, 62.87; H, 7.56; N, 4.87.

Example 1404



(4R-cis)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentanoic acid

Step 1: Preparation of ester intermediate

A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.0 g, 2.2 mmol, obtained from Example 1402, Step 10) in acetone (10 mL) at 25 °C under N_2 was treated with powdered K_2CO_3 (0.45 g, 3.3 mmol, 1.5 eq.), benzyl 5-

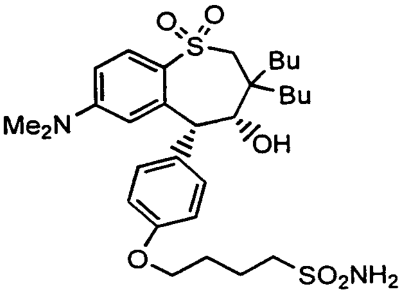
bromovalerate (0.88 g, 3.3 mmol, 1.5 eq.) and a catalytic amount of tetra-*n*-butylammonium iodide (2 mg), and the resulting solution was stirred at 65 °C for 24 hours. The pale amber slurry was cooled to 25 °C and was concentrated in vacuo to provide a yellow residue. Purification by flash chromatography (2.4 x 30 cm silica, 20-40% EtOAc/hexane) afforded the ester intermediate (1.2 g, 86%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.64 (m, 1H), 1.86 (m, 2H), 2.21 (m, 1H), 2.47 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, *J* = 15.1 Hz, *J* = 47.7 Hz, 2H), 4.10 (d, *J* = 7.9 Hz, 1H), 5.13 (s, 2H), 5.47 (s, 1H), 6.00 (d, *J* = 2.5 Hz, 1H), 6.50 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.36 (m, 5H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for $C_{38}H_{51}NO_6S$: 650.3515. Found: 650.3473.

Step 2: Preparation of acid

A solution of the ester intermediate (0.99 g, 1.5 mmol, obtained from Step 1) in ethanol (7.5 mL) at 25 °C was treated with 5% palladium on carbon (0.15 g, 10 wt %) then stirred under an atmosphere (1 atm) of H_2 via hydrogen balloon. Every 10 min, hydrogen gas was bubbled through the slurry for 1 min, for a total reaction time of 4 hours. The slurry was placed under an atmosphere of N_2 and nitrogen was bubbled through the reaction mixture for 10 min. The mixture was filtered through a plug of Celite® (10 g) and concentrated in vacuo to give a white foam. Purification by flash chromatography (2.6 x 25 cm silica, 1.5% EtOH/CH_2Cl_2) afforded the desired title compound (0.54 g, 63%) as a white foam: mp: 76-79 °C; ^1H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.10-1.46 (br m, 10H), 1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, *J*

= 15.1 Hz, *J* = 49.7 Hz, 2H), 4.00 (s, 2H), 4.09 (s, 1H), 5.45 (s, 1H), 5.99 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.39 (m, 5H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for $C_{31}H_{45}NO_6S$: 560.3046. Found: 560.3043.

Example 1405



(4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy-1-butanesulfonamide

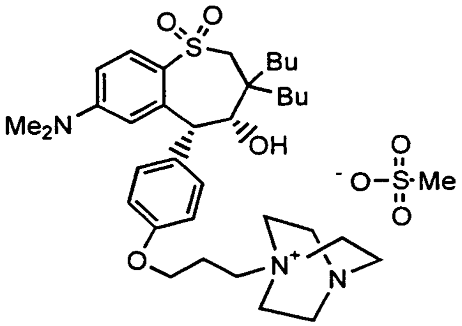
Step 1: Preparation of sulfonic acid intermediate

A solution of 7.4 g (16.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in acetone (35 mL) at 25 °C under N_2 was treated with powdered potassium carbonate (3.3 g, 24.1 mmol, 1.5 equiv.) and 1,4-butane sultone (2.5 mL, 24.1 mmol, 1.5 equiv.) and stirred and heated at 65 °C for 64 h. The solution was allowed to cool to 25 °C and quenched by the addition of water (50 mL), until a homogeneous mixture was obtained. The clear and colorless solution was added dropwise to a 4 N HCl solution cooled to 0 °C over a 30 min period. The mixture was vigorously stirred for 4 h then allowed to warm to ambient temperature and stirred for an additional 16 h. The resultant white precipitate was filtered and washed with water and dried in vacuo to provide 8.8 g (92%) of the desired sulfonic acid as a white solid. A portion of the white solid was recrystallized from CH_3CN/hexane to give the desired sulfonic acid as colorless needles: mp 229-236 °C (decomposed); ^1H NMR (DMSO-d_6) δ 0.82 (m, 6H), 1.02-1.33 (br m, 10H), 1.59 (m, 1H), 1.73 (m, 4H), 2.00 (s, 1H), 2.48 (m, 2H), 2.71 (s, 6H), 2.98 (s, 1H), 3.86 (s, 1H), 3.93 (m, 2H), 5.08 (s, 1H), 5.89 (s, 1H), 6.52 (dd, J = 8.9, 2.4 Hz, 1H), 6.92 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.9 Hz, 1H); Anal. Calc'd for $C_{30}H_{45}NO_7S_2$: C, 60.48; H, 7.61; N, 2.35. Found: C, 60.53; H, 7.70; N, 2.42.

Step 2: Preparation of 7-(dimethylamino)-benzothiepin-5-yl]phenoxy-1-butanesulfonamide

To a solution of 1.12 g (1.88 mmol) of the sulfonic acid (obtained from Step 1) in 10 mL CH_2Cl_2 was added 785 mg (3.77 mmol) PCl_5 and stirred for 1 hour. Water was added and the mixture was extracted and washed with brine. Dried with $MgSO_4$, filtered and solvent evaporated. To the residue was added 30 mL of 0.5M NH_3 in dioxane and stirred 16 hours. The precipitate was filtered and the solvent evaporated. The residue was purified by MPLC (33% EtOAc in hexane) to afford the desired title compound as a beige solid (125 mg, 11%): mp 108-110 °C; ^1H NMR ($CDCl_3$) δ 0.85-0.93 (m, 6H), 1.13-1.59 (m, 10H), 1.60-1.67 (m, 1H), 1.94-2.20 (m, 5H), 2.82 (s, 6H), 2.99 (d, J = 15.3 Hz, 1H), 3.15 (t, J = 15.3 Hz, 1H), 3.23 (t, J = 7.7 Hz, 2H), 4.03 (t, J = 5.8 Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (s, 2H), 5.47 (s, 1H), 6.02 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 1H). HRMS. Calc'd for $C_{30}H_{47}N_2O_6S_2$: 595.2876. Found: 595.2874.

Example 1406



(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-azoniabicyclo[2.2.2]octane, methanesulfonate (salt)

Step 1: Preparation of dimesylate intermediate

To a cooled (-20 °C) solution of 5.0 g (65.7 mmol) of 1,3-propanediol in 50 mL of triethylamine and 200 mL of methylene chloride was added 15.8 g (137.9 mmol) of methanesulfonyl chloride. The mixture was stirred for 30 minutes, then warmed to ambient temperature and partitioned between ethyl acetate and 1N HCl. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 13.5 g (89%) of dimesylate intermediate as a clear yellowish oil: ^1H NMR ($CDCl_3$) δ 2.12 (quintet, *J* = 4.5 Hz, 4H), 3.58 (s, 6H), 4.38 (t, *J* = 5.4 Hz)

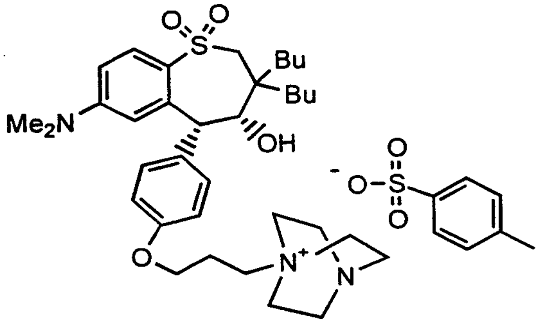
Step 2: Preparation of propyl mesylate intermediate

To a solution of 2.4 g (5.2 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 6.0 g (26.1 mmol) of dimesylate intermediate (obtained from Step 1) in 50 mL of acetone was added 3.6 g (26.1 mmol) of K_2CO_3. The reaction was heated to reflux overnight then cooled to ambient temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 36% ethyl acetate/hexanes afforded 2.8 g (90%) of the propyl mesylate intermediate as a white foam: ^1H NMR ($CDCl_3$) δ 0.86-0.95 (m, 6H), 1.06-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.14-2.32 (m, 3H), 2.84 (s, 6H), 3.02 (s, 3H), 3.08 (AB_q, J_{AB} = 15.0 Hz, J = 46.9 Hz, 4.09-4.18 (m, 3H), 4.48 (t, J = 6.0 Hz, 2H), 5.49 (s, 1H), 6.11 (s, 1H), 6.65 (d, J = 8.7 Hz, 1H), 6.94(d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H).

Step 3: Preparation of quaternary salt

To a solution of 1.2 g (2.0 mmol) of propyl mesylate intermediate (obtained from Step 2) in 20 ml of acetonitrile was added 0.3g (2.9 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction mixture was stirred at 60 °C for three hours, then cooled to ambient temperature and concentrated in vacuo. Purification by trituration with methylene chloride/ethyl ether gave 1.3 g (91%) of the desired title compound as a white solid: mp. (dec) 230-235 °C; ^1H NMR ($CDCl_3$) δ 0.86-0.95 (m, 6H), 1.04-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.25 (m, 3H), 2.28-2.39 (m, 2H), 2.83 (s, 6H), 3.04 (s, 3H), 3.09 (AB_q, J_{AB} = 15.6 Hz, J = 42.2 Hz, 2H) 3.22-3.32 (m, 6H), 3.56-3.66 (m, 6H), 3.73-3.83 (m, 2H), 4.06-4.17 9m, 3H), 5.47 (s, 1H), 5.97 (s, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.90(d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.9 Hz, 1H). MS (ES+) *m/e* 612.4. HRMS (ES+) Calc'd for $C_{35}H_{54}N_3O_4S^+$: 612.3835. Found: 612.3840.

Example 1407



(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-azoniabicyclo[2.2.2]octane,4-methylbenzenesulfonate (salt)

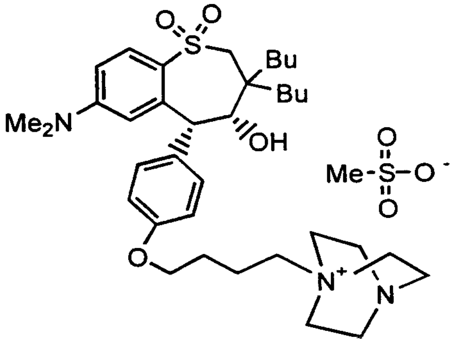
Step 1: Preparation of propyl tosylate intermediate

A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N_2 was treated with powdered K_2CO_3 (3.8 g, 27.2 mmol, 2.5 eq.) and 1,3-propanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting mixture was stirred at 65 °C for 21 hours. The cream-colored slurry was cooled to 25 °C and was filtered through a sintered glass funnel. The filtrate was concentrated and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 150 mL) and saturated aqueous NaCl (2 x 150 mL), and was dried ($MgSO_4$) and concentrated in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 x 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl tosylate intermediate (6.0 g, 80%) as a white foam: ^1H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.63 (m, 1H), 2.14 (m, 2H), 2.21 (m, 1H), 2.41 (s, 3H), 2.81 (s, 6H), 3.06 (ABq, J = 15.1 Hz, J = 49.0 Hz, 2H), 4.01 (t, J = 5.3 Hz, 2H), 4.10 (m, 1H), 4.26 (t, J = 5.9 Hz, 2H), 5.29 (s, 1H), 5.48 (s, 1H), 5.98 (s, 1H), 6.51 (dd, J = 8.9, 1.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of quaternary salt

A solution of the propyl tosylate intermediate (1.05 g, 1.56 mmol, obtained from Step 1) in acetonitrile (15 mL) at 25 °C under N_2 was treated with diazabicyclo[2.2.2]octane (DABCO, 0.26 g, 2.34 mmol, 1.5 eq.) and stirred at 50 °C for 6 hours, then at 25 °C for 14 hours. The pale amber solution was cooled to 25 °C and concentrated in vacuo to provide an amber oil. The residue was dissolved in a minimal amount of CH_2Cl_2 (5 mL) and diluted with Et_2O (100 mL) while vigorously stirring for 4 hours, during which time a white solid precipitated. The white solid was collected (Et_2O wash) to give the desired title compound (1.11 g, 90%) as a white amorphous solid: mp 136.5-142 °C (decomposed); ^1H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.12-1.43 (br m, 9H), 1.61 (m, 1H), 1.65 (m, 1H), 2.18 (m, 1H), 2.22 (m, 2H), 2.27 (s, 3H), 2.78 (s, 6H), 3.07 (ABq, J = 15.1 Hz, J = 39.5 Hz, 2H), 3.49 (br s, 6H), 3.68 (m, 1H), 3.74 (br s, 6H), 3.96 (br s, 2H), 4.09 (d, J = 7.3 Hz, 1H), 5.46 (s, 1H), 5.96 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for $C_{35}H_{54}N_3O_4S$: 612.3835. Found: 612.3832.

Example 1408



(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-azoniabicyclo[2.2.2]octanemethanesulfonate (salt)

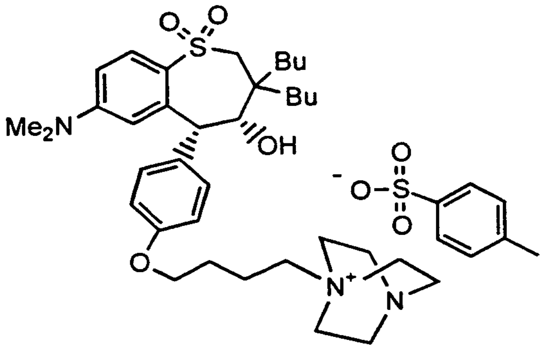
Step 1: Preparation of butyl mesylate intermediate

A mixture of 1.00 g (2.18 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88 mmol) of potassium carbonate in 20 mL of acetone was stirred at reflux overnight. The mixture was concentrated in vacuo and the crude was dissolved in 30 mL of ethyl acetate. The insoluble solid was filtered off and the filtrate was concentrated in vacuo. The resulting white foam was chromatographed through silica gel column, and eluted with 30% ethyl acetate/hexane to give 1.02 g (77%) of butyl mesylate intermediate as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.20-1.67 (m, 12H), 1.98 (m, 4H), 2.22 (m, 1H), 2.83 (s, 6H), 3.04 (s, 3H), 3.08 (ABq, 2H), 4.05 (t, *J* = 5.55 Hz, 2H), 4.11 (d, *J* = 6.90 Hz, 1H), 4.35 (t, *J* = 6.0 Hz, 2H), 5.49 (s, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 9.0 Hz, 2.7 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 1H).

Step 2: Preparation of ester intermediate

A solution of 520 mg (0.85 mmol) of butyl mesylate intermediate (obtained from Step 1) and 191 mg (1.71 mmol) of DABCO in 10 mL of acetonitrile was stirred at 80 °C for 4 hours. The reaction mixture was concentrated in vacuo to yield a white foam. The foam was crushed and washed with ether. The solid was filtered off and dried in vacuo to give 540 mg (88%) of the desired title compound which was recrystallized from methylene chloride and acetone as a white solid: mp 248-251 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.14-1.47 (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H), 2.77 (s, 3H), 2.82 (s, 3H), 3.07 (ABq, 2H), 3.26 (t, *J* = 7.1 Hz, 6H), 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (s, 1H), 5.99 (d, *J* = 2.4 Hz, 1H), 6.51 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 1H).

Example 1409



(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-azoniabicyclo[2.2.2]octane-4-methylbenzenesulfonate (salt)

Step 1: Preparation of propyl tosylate intermediate

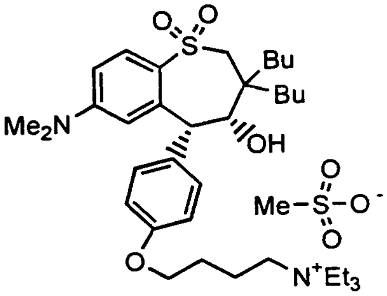
A solution of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N_2 was treated with powdered K_2CO_3 (3.8 g, 27.2 mmol, 2.5 eq.) and 1,4-butanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting solution was stirred at 65 °C for 21 hours. The cream-colored slurry was cooled to 25 °C and filtered through a sintered glass funnel. The filtrate was concentrated and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 150 mL) and saturated aqueous NaCl (2 x 150 mL). The extract was dried ($MgSO_4$) and concentrated in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 x 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl tosylate intermediate (6.0 g, 80%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.10-1.44 (br m, 10H), 1.61 (m, 1H), 1.84 (m, 4H), 2.19 (m, 1H), 2.43

(s, 3H), 2.80 (s, 6H), 3.03 (ABq, *J* = 15.1 Hz, *J* = 46.3 Hz, 2H), 3.93 (m, 2H), 4.06-4.13 (m, 4H), 5.44 (s, 1H), 5.96 (s, 1H), 6.46 (dd, *J* = 8.9, 1.4 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.83 (m, 1H).

Step 2: Preparation of quaternary salt

A solution of propyl tosylate intermediate (5.8 g, 8.5 mmol, obtained from Step 1) in acetonitrile (100 mL) at 25 °C under N_2 was treated with diazabicyclo[2.2.2]octane (DABCO, 1.1 g, 10.1 mmol, 1.2 eq.) and stirred at 45 °C for 6 hours. The pale yellow solution was cooled to 25 °C and concentrated in vacuo to provide an off-white solid. The residue was dissolved in a minimal amount of CH_2Cl_2 (5 mL) and diluted with Et_2O (100 mL) while vigorously stirring for 3 hours, during which time a white solid precipitated. The white solid was collected and recrystallized from EtOAc/hexane to give the desired title compound (5.7 g, 85%) as colorless needles: mp 223-231 °C (decomposed); ^1H NMR ($CDCl_3$) δ 0.86 (m, 6H), 1.09-1.43 (br m, 12H), 1.61-1.90 (br m, 5H), 2.13 (m, 1H), 2.25 (s, 3H), 2.75 (s, 6H), 3.03 (ABq, *J* = 15.1 Hz, *J* = 30.0 Hz, 2H), 3.05 (br s, 6H), 3.37 (br s, 6H), 3.89 (m, 2H), 4.07 (d, *J* = 7.5 Hz, 1H), 5.39 (s, 2H), 5.97 (d, *J* = 1.6 Hz, 1H), 6.44 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for $C_{36}H_{56}N_3O_4S$: 626.3992. Found: 626.3994. Anal. Calc'd for $C_{43}H_{63}N_3O_7S_2$: C, 64.71; H, 7.96; N, 5.27. Found: C, 64.36; H, 8.10; N, 5.32.

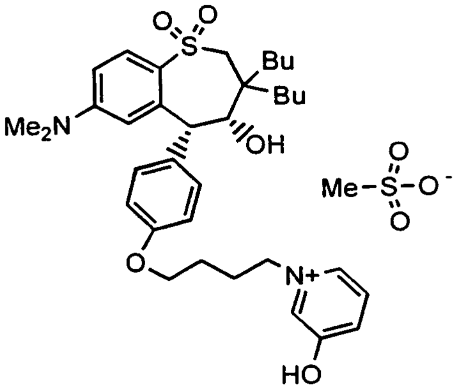
Example 1410



(4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]-N,N,N-triethyl-1-butanaminium

A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 15 mL of triethylamine in 10 mL of acetonitrile was heated at 50 °C for 2 days. The solvent was evaporated and the residue was triturated with ether and ethyl acetate to afford 500 mg (43%) of product as a semi-solid. ^{1}H NMR ($CDCl_3$) δ 0.8 (m, 6 H), 1-1.6 (m, 24 H), 2.1 (m, 1 H), 2.6 (s, 3 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.0 (d, J = 15 Hz, 1 H), 3.3 (m, 8 H), 4.0 (m, 4 H), 5.3 (s, 1 H), 5.9 (s, 1 H), 6.4 (m, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS *m/e* 615.

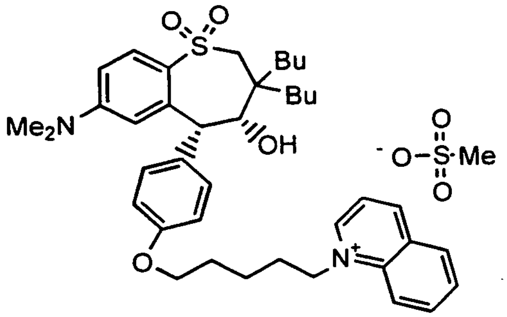
Example 1411



(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-3-hydroxypyridinium, methanesulfonate (salt)

A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 234 mg (2.46 mmol) of 3-hydroxy pyridine in 1 mL of dimethylformamide was heated at 70 °C for 20 hours. The solvent was evaporated and the residue was triturated with ether and ethyl acetate to afford 990 mg (86%) of product as a semi-solid: ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 6 H), 1-1.5 (m, 10 H), 1.7 (m, 1 H), 1.9 (m, 2 H), 2-2.4 (m, 3 H), 2.9 (s, 6 H), 3.1 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 4.1 (m, 3 H), 4.7 (m, 2 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.7 (m, 1 H), 8.0 (m, 2 H), 8.2 (m, 1 H), 9.1 (s, 1 H). MS *m/e* 609.

Example 1412



(4R-cis)-1-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]quinolinium, methanesulfonate (salt)

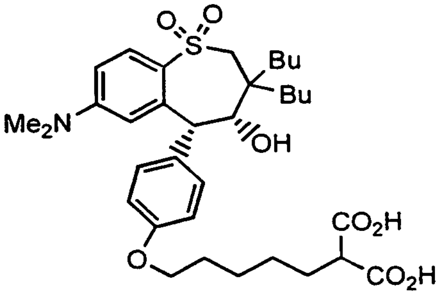
Step 1: Preparation of pentyl mesylate intermediate

To a stirred solution of 231 mg (5.79 mmol, 60% disp.) of NaH in 22 mL of DMF was added 2.05g (4.45 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the mixture was added 18.02 g (55.63 mmol) of 1,5-diiodopentane and the solution was stirred overnight at ambient temperature. DMF was removed by high vacuum and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the pentyl mesylate intermediate: ^1H NMR ($CDCl_3$) δ 0.90(q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6h), 3.0 (q, 2H), 3.22 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.1 (d, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of quaternary salt

To 1.0g (1.53 mmol) of the pentyl mesylate intermediate (obtained from Step 1) was added 3.94 g (30.5 mmol) of quinoline and 30 mL of acetonitrile. The solution was heated at 45 °C under N_2 for 10 days. The concentrated residue was purified by reverse phase C18 column chromatography. The obtained material was exchanged to its mesylate anion by ion exchange chromatography to give the desired title compound as a solid: mp 136 °C; ^{1}H NMR ($CDCl_3$) δ 0.95(q, 6H), 1.05-2.25 (m, 18H), 2.8 (s, 9H), 3.0 (q, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.28 (t, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.4 (d, 2H), 7.82 (d, 1H), 7.9 (t, 1H), 8.2 (t, 2H), 8.3 (q, 2H), 8.98 (d, 1H), 10.2 (d, 1H). HRMS. Calc'd for $C_{40}H_{53}N_2O_4S$: 657.3726. Found: 657.3736. Anal. Calc'd for $C_{40}H_{53}N_2O_4S.CH_3O_3S$: C, 65.40; H, 7.50; N, 3.72; S, 8.52. Found: C, 62.9; H, 7.42; N, 3.56; S, 8.41.

Example 1413



(4S-cis)-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]propanedioic acid

Step 1: Preparation of pentyl bromide intermediate

To a stirred solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was added 6.0 g (13.1 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and the mixture was stirred overnight at ambient temperature. DMF was removed _in vacuo_ and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

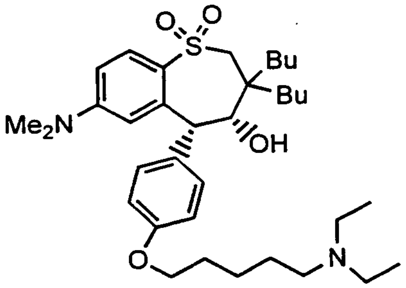
Step 2: Preparation of dibenzyl ester intermediate

To the mixture of 59 mg (1.476 mmol, 60% disp) of NaH in 27 mL of THF and 9 mL of DMF at 0 °C was added 0.84 g (2.952 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min. To the solution was added 0.5987 g (0.984 mmol) of the pentyl bromide intermediate, and the mixture was stirred at 80 °C overnight. Solvent was removed _in vacuo_, and the residue was extracted with methylene chloride and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the dibenzyl ester intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 1H), 3.9 (t, 2H), 4.1 (d, 1H), 5.18 (s, 4H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 12H), 7.85 (d, 1H).

Step 3: Preparation of diacid

A suspension of 0.539 g (0.664 mmol) of the dibenzyl ester intermediate (obtained from Step 2) and 25 mg of 10% Pd/C in 30 mL of ethanol was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 6H), 1.05-2.2 (m, 20H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 1H), 3.95 (s, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.85 (d, 1H). HRMS. Calc'd for $C_{34}H_{49}NO_8S$: 632.3257. Found: 632.3264. Anal. Calc'd for $C_{34}H_{49}NO_8S$: C, 64.63; H, 7.82; N, 2.22; S, 5.08. Found: C, 63.82; H, 7.89; N, 2.14; S, 4.93.

Example 1414



(4R-cis)-3,3-Dibutyl-5-[4-[[5-(diethylamino)pentyl]oxy]phenyl]-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

Step 1: Preparation of pentyl iodide intermediate

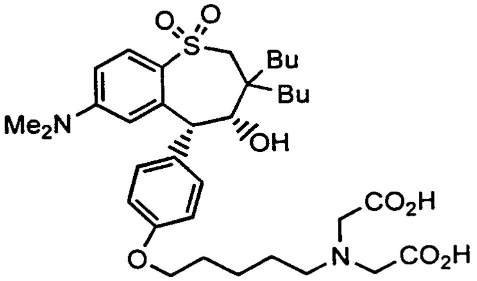
To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (3 g, 6.53 mmol, obtained from Example 1402, Step 10) in 100 mL of dimethylformamide was added 198 mg (7.83 mmol) of 95% sodium hydride. The mixture was stirred 15 minutes at room temperature and diiodopentane was added. After one hour at room temperature the mixture was diluted in ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with hexane/ethyl acetate (1/5) to afford 2.92g (4.46 mmol) of the pentyl iodide intermediate: ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 6 H), 1-1.5 (m, 11 H), 1.6 (m, 3 H), 1.8 (m, 4 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.9 (d, J = 7 Hz, 1 H).

Step 2: Preparation of amine

A solution of 550 mg (0.76 mmol) of the pentyl iodide intermediate (obtained from Step 1) and 279 mg (3.81 mmol) of diethylamine in 3 mL of acetonitrile was stirred at 100 °C overnight. The mixture was concentrated in vacuo to yield a yellowish brown foam. The foam was dissolved in 10 mL of ethyl acetate and washed with 50 mL of saturated sodium carbonate solution twice. The ethyl acetate layer was dried over magnesium sulfate and concentrated to yield 390 mg (85%) of the desired title compound as a yellow foamy solid: ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.20-1.47 (m, 12H), 1.53-1.67 (m, 4H), 1.76-1.90 (m, 8H), 2.21 (m,

1H), 2.74-2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, J = 6.3 Hz, 2H), 4.10 (d, J = 7.8 Hz, 1H), 5.48 (s, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H).

Example 1415



(4R-cis)-N-(Carboxymethyl)-N-[5-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine

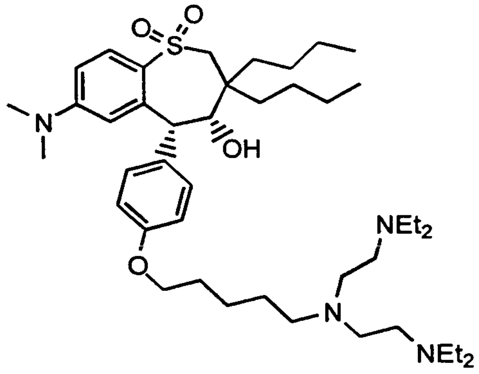
Step 1: Preparation of diester intermediate

A mixture of 8.6 g (14.1 mmol) of pentyl bromide intermediate (obtained from Example 1413, Step 1), 65 g (0.35 mol) of diethylaminodiacetate and 7.5 g (71 mmol) of anhydrous Na_2CO_3 was stirred at 160 °C for 3 hours. The reaction mixture was diluted with water and extracted with methylene chloride. The volatiles was removed in vacuo to give 9.6g (95%) of the diester intermediate. ^1H NMR spectrum was consistent with the structure; MS (M+H) *m/e* 717.

Step 2: Preparation of diacid

The mixture of the diester intermediate (obtained from Step 1) and 2.7g (64.3 mmol) of LiOH in THF (75 mL) and water (50 mL) was stirred at 40 °C for 18 hours. The reaction mixture was acidified with 1% HCl and extracted with dichloromethane. The residue was triturated with hexane, filtered to give 8.9g (93%) of the desired title compound as a solid: mp 148-162 °C; ^{1}H NMR (CD_3OD) δ 0.92 (t, 6H), 1.1-1.9 (m, 31H), 2.15 (t, 1H),2.8(s, 6H), 3.15 (ABq, 2H), 3.75(m, 1H), 4.1 (m, 6H), 5.3(s, 1H), 6.1 (s, 1H), 6.6 (d, 1H), 7.0(d, 2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M+H) *m/e* 661. Anal. Calc'd for [$C_{35}H_{52}N_2O_8S$ + $1.5H_2O$]: C,61.11; H,8.06; N,4.07; S,4.66. Found: C,61.00; H,7.72; N,3.89; S,4.47.

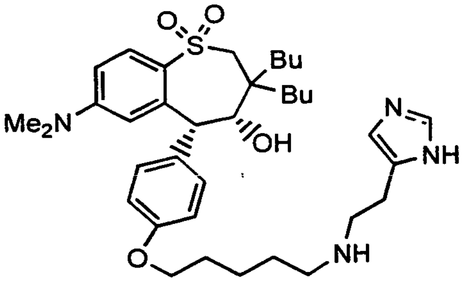
Example 1416



(4R-cis)-5-[4-[[5-[bis[2-(Diethylamino)ethyl]amino]pentyl]oxy]phenyl]-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) in N,N,N',N'-tetraethyl diethylenetriamine was heated to 80 °C for 4 hours. The mixture was dissolved in ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by reverse phase chromatography. The fractions containing the product were concentrated in vacuo, dissolved in ethyl acetate and washed with saturated $NaHCO_3$. The residue was dried and concentrated in vacuo to afford 840 mg (74%) of the desired title compound as a thick oil. ^1H NMR ($CDCl_3$) δ 0.8 (m, 6 H), 1-1.6 (m, 28 H), 1.8 (m, 2 H), 2.1 (m, 1 H), 2.5 (m, 18 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.1 (d, J = 15 Hz, 1 H), 3.9 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.4 (s, 1 H), 6.0 (s, 1 H), 6.4 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS (M+H) *m/e* 743.

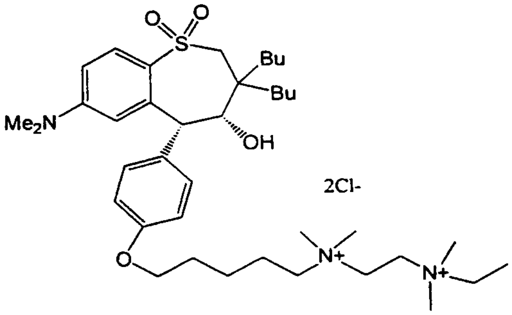
Example 1417



(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-[[2-(1H-imidazol-4-yl)ethyl]amino]pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) and 3.4 g (30.6 mmol) of histamine was heated to 50 °C for 17 hours. The mixture was dissolved in ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with ether to afford 588 mg (60%) of the desired title compound as a semi-solid: ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 6 H), 1-1.7 (m, 14 H), 1.9 (m, 3 H), 2.0 (m, 2 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (m, 3 H), 3.2 (m, 2 H), 4.0 (m, 2 H), 4.1 (m, 3 H), 5.5 (s, 1 H), 6.0 (s, 1 H), 6.5 (m, 1 H), 6.8 (s, 1 H), 6.9 (d, *J* = 9 Hz, 2 H), 7.4 (m, 3 H), 7.9 (d, *J* = 8 Hz, 1 H). MS (M+H) *m/e* 639.

Example 1418



(4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N′-ethyl-N,N,N′,N′-tetramethyl-1,2-ethanediaminium dichloride

Step 1: Preparation of pentyl bromide intermediate

A mixture of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.680g, 3.66 mmol, obtained from Example 1402, Step 10) and sodium hydride (0.250g, 6.25 mmol) in 30 mL of DMF was stirred in a dry 100 mL round-bottom flask under N_2. To this solution was added 1,5-dibromopentane (6.0 mL/44.0 mmol), and the resulting mixture was stirred for 18 hours. The reaction was diluted with brine (100 mL) and H_2O (20 mL), and the mixture was extracted with EtOAc (3x50 mL). Organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by filtration through silica gel eluting with 20% EtOAc/hexane and evaporation in vacuo gave pentyl bromide intermediate as a white foamy solid (1.783g, 80%): ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.56 (m, 10H), 1.58-1.70 (m, 3H), 1.78-2.03 (m, 4H), 2.15-2.24 (m, 1H), 2.77 (s, 1H), 2.80 (s, 6H), 3.05 (ABq, 2H), 3.42 (t, 2H), 3.98 (t, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 5.99 (d, 1H), 6.50 (dd, 1H), 6.91 (d, 2H), 7.40 (d, 2H), 7.88 (d, 1H).

Step 2: Preparation of mono-quaternary salt

The mixture of pentyl bromide intermediate (0.853g, 1.40 mmol, obtained from Step 1), N,N,N',N'-tetramethylethylenediamine (1.0 mL/6.62 mmol) in 30 mL of acetonitrile was stirred at 40 °C for 12 hours, and the reaction mixture was concentrated in vacuo to give an off-white foamy solid (1.052g). The crude product was dissolved in acetonitrile (1.5 mL) and triturated with ethyl ether. The solvent was decanted to yield a sticky solid. This trituration method was repeated twice, and the resulting sticky solid was concentrated in vacuo to give the mono-quaternary salt as an off-white foamy solid (0.951g, 94%): ^1H NMR ($CDCl_3$) δ 0.81 (t, 6H), 0.96-1.64 (m, 13H), 1.62-1.85 (m, 4H), 2.03-2.18 (m, 1H), 2.20 (s, 6H), 2.67 (t, 2H), 2.74 (s, 6H), 2.98 (ABq, 2H), 3.30-3.42 (m, 1H), 3.38 (s, 6H), 3.60-3.75 (m, 4H), 3.90 (t, 2H), 4.01 (s, 1H), 5.37 (s, 1H), 5.92 (s, 1H), 6.41 (dd, 1H), 6.81 (d, 2H), 7.32 (d, 2H), 7.77 (d, 1H).

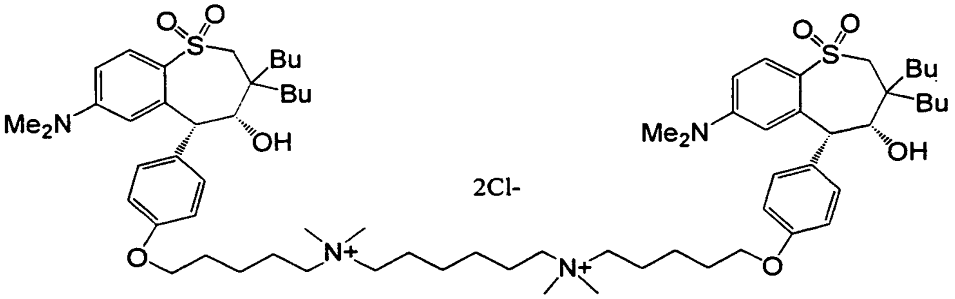
Step 3: Preparation of di-quaternary salt

The mono-quaternary salt (0.933g, 1.29 mmol, obtained from Step 2), iodoethane (0.300 mL/3.75 mmol), and acetonitrile (30.0 mL) were combined in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N_2, sealed, equipped with magnetic stirrer, and heated to 50 ^{0}C. After 24 hours, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give a yellow foamy solid (1.166g). The solid was dissolved in methylene chloride/acetonitrile and precipitated with ethyl ether. After cooling to 0 ^{0}C overnight, the resulting solid was filtered, washed with ethyl ether and concentrated *in vacuo* to yield the di-quaternary salt as an off-white solid (1.046g, 92%): ^{1}H NMR (CD_3OD) δ 0.59 (t, 6H), 0.70-1.10 (m, 9H), 1.16 (t, 3H), 1.22-1.80 (m, 9H), 2.42 (s, 6H), 2.78 (d, 2H), 2.98 (s, 6H), 3.02 (s, 6H), 3.22-3.37 (m, 4H), 3.63-3.78 (m, 4H), 3.80 (s, 4H), 4.93 (s, 1H), 5.71 (s, 1H), 6.22 (dd, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.40 (d, 1H).

Step 4: Preparation of quaternary di-chloride salt

The iodobromosalt (obtained from Step 3) was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H_2O/acetonitrile to give the desired title compound as a white foamy solid (0.746g, 84%): mp 193.0-197.0 °C; ^{1}H NMR (CD_3OD) δ 0.59 (t, *J* = 6.0 Hz, 6H), 0.70-1.12 (m, 9H), 1.16 (t, *J* = 6.6 Hz, 3H), 1.24-1.90 (m, 9H), 2.50 (s, 6H), 2.78 (s, 2H), 3.08 (s, 6H), 3.11 (s, 6H), 3.24-3.50 (m, 4H), 3.68 (s, 2H), 3.81 (s, 2H), 4.16 (s, 4H), 5.02 (s, 1H), 5.72 (s, 1H), 6.19 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 1H). HRMS. Calc'd for $C_{39}H_{67}N_3O_4SCl$: 708.4541. Found: 708.4598.

Example 1419

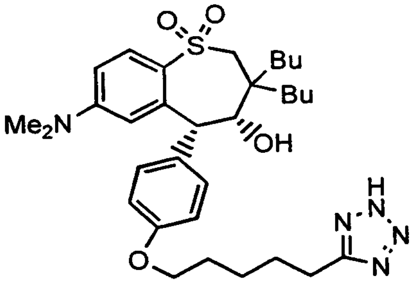


[4R-[4a,5a(4R*,5R*)]]-N,N'-bis[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N,N,N'N'-tetramethyl-1,6-hexanediaminium dichloride

The pentyl bromide intermediate (1.002g, 1.64 mmol, obtained from Example 1418, Step 1) and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100g, 0.580 mmol) in 5 mL of acetonitrile were placed in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N_2, sealed, equipped with magnetic stirrer and heated to 50 °C. After 15 hours, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give an off-white foamy solid (1.141g). The solid was dissolved in acetonitrile and precipitated with ethyl ether. After cooling to 0 °C, the solvent was decanted to yield a sticky off-white solid. This trituration method was repeated, and the resulting sticky solid was concentrated *in vacuo* to give the desired dibromide salt as an off-white foamy solid (0.843g, quantitative): ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 12H), 1.01-1.70 (m, 30H), 1.76-2.08 (m, 12H), 2.18 (t, *J* =

12.3 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.35 (s, 12H), 3.52 (br s, 6H), 3.72 (br s, 4H), 3.97 (br s, 4H), 4.08 (br s, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.51 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 4H), 7.38 (d, *J* = 7.8 Hz, 4H), 7.83 (d, *J* = 8.7 Hz, 2H). The dibromide salt was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H_2O/CH_3CN to give the desired title compound as a white foamy solid (0.676g, 86%): mp 178.0-182.0 °C; ^1H NMR ($CDCl_3$) δ 0.80-0.90 (m, 12H), 1.01-1.70 (m, 30H), 1.75-2.06 (m, 12H), 2.16 (t, *J* = 12.9 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.33 (s, 12H), 3.49 (br s, 6H), 3.70 (br s, 4H), 3.96 (t, *J* = 5.4 Hz, 4H), 4.08 (s, 2H), 5.42 (s, 2H), 5.986 (s, 1H), 5.993 (s, 1H), 6.49 (d, *J* = 9.0 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 4H), 7.38 (d, *J* = 8.1 Hz, 4H), 7.84 (d, *J* = 8.7 Hz, 2 H). HRMS. Calc'd for $C_{36}H_{58}N_2O_4S$: 614.4118. Found: 614.4148.

Example 1420



(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-(1H-tetrazol-5-yl)pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

Step 1: Preparation of pentyl bromide intermediate

To a stirred suspension of 1.01 g (25.4 mmol, 60% oil dispersion) of sodium hydride in 150 mL of DMF was added 9.0g (19.5 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in portions. After 30 minutes the reaction was cooled in a water bath (15 °C) and 4.48 g (195 mmol) of 1,5-dibromopropane was added. The reaction was stirred at ambient temperature for 1.5 hours and quenched with 50 mL of saturated NH_4Cl. The reaction was diluted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 25% ethyl acetate/hexanes afforded 10.17 g (85%) of the pentyl bromide intermediate as a colorless foam: mp 65-70 °C; ^1H NMR ($CDCl_3$) δ 0.84-0.98 (M, 6H), 1.04-1.52 (m, 10H), 1.58-1.65 (m, 3H), 1.82 (p, J = 6.8 Hz, 2H), 1.94 (p, J = 7.0 Hz, 2H), 2.12-2.26 (m, 1H), 2.82 (s, 6H), 3.06 (AB_q, J_{AB} = 15.2, 45.3 Hz, 2H), 3.44 (t, J = 6.7 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 6.15 (d, J = 2.7 Hz, 1H), 6.68 (dd, J = 2.5, 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.7 Hz, 1H).

Step 2: Preparation of pentyl nitrile intermediate

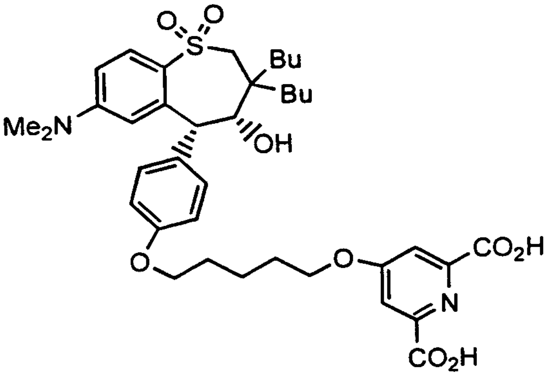
To a stirred solution of 378 mg (0.621 mmol) of the pentyl bromide intermediate (obtained from Step 1) in 1 mL of DMSO was added 37 mg (0.745 mmol) of sodium cyanide. The reaction was stirred at ambient temperature for 16 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 278 mg

(93% RPHPLC purity, ca. 75%) of the pentyl nitrile intermediate as a colorless foam: ^{1}H NMR ($CDCl_3$) δ .0.86-0.96 (m, 6H), 1.02-1.21(m, 1H), 1.21-1.52 (m, 19H), 1.58-1.92 (m, 7H), 2.16-2.28 (m, 1H), 2.41 (t, *J* = 6.9 Hz, 2H), 2.83 (s, 6H), 3.08 (AB_q, 15.0, 47.5 Hz, 2H), 4.01 (t, *J* = 6.2 Hz, 2H), 4.1 (s, 1H), 5.49 (s, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 6.59 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 1H). MS (ES, M+H) *m/e* 555.

Step 3: Preparation of tetrazole

A solution of 275 mg (0.5 mmol) of the nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene was stirred with heating at 80 °C for 60 hours. The reaction was concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 226 mg of the desired title compound (75%) as a colorless foam: mp 80-85 °C; ^{1}H NMR ($CDCl_3$) δ 0.83-0.95 (m, 6H), 1.30-1.52 (m, 10H), 1.52-1.73 (m, 3H), 1.79-1.99 (m, 4H), 2.14-2.26 (m, 1H), 2.91 (s, 6H), 3.02-3.22 (m, 4H), 3.92-4.06 (m, 2H), 4.16 (s, 1H), 5.47 (s, 1H), 6.28 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 2.7, 8.8 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 1H). HRMS Calc'd for $C_{32}H_{48}N_5O_4S$: 598.3427. Found: 598.3443.

Example 1421



(4R-cis)-4-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-1benzothiepin-5-yl]phenoxy]pentyl]oxy]-2,6-pyridinecarboxylic acid

Step 1: Preparation of pentyl bromide intermediate

To a solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was add 6.0g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and stirred overnight at ambient temperature. DMF was removed *in vacuo* and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Esterification of chelidamic acid

A solution of 10 g (54.6 mmol) of chelidamic acid, 23.0 g (120.12 mmol) of 1-(3-dimethyl amino propyl)-3 ethyl carbodiimide hydrochloride, 1.33 g (10.8 mmol) of 4-dimethyl amino pyridine, and 12.4 mL (120.12 mmol) of benzyl alcohol in 100 mL of DMF was stirred at ambient temperature overnight under N_2. DMF was removed in vacuo and the residue was extracted with methylene chloride, washed with 5% $NaHCO_3$, 5% acetic acid, H_2O, and brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give dibenzyl chelidamic ester: ^{1}H NMR ($CDCl_3$) δ 5.4 (s, 4H), 7.4 (m, 12H).

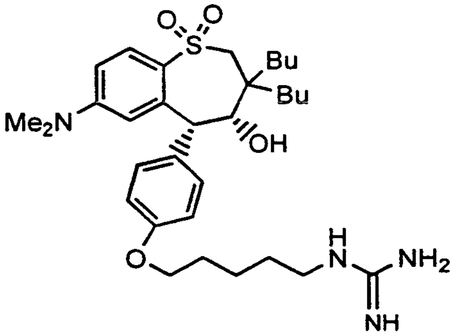
Step 3: Preparation of pyridinyl benzyl ester intermediate

A solution of 79 mg (1.972 mmol, 60% disp) of NaH and 0.716g (1.972 mmol) of dibenzyl chelidamic ester (obtained from Step 2) in 17.5 mL of DMF was stirred at ambient temperature for 1 hour. To the solution was added 1.0 g (1.643 mmol) of the pentyl bromide intermediate and the mixture was stirred under N_2 overnight at 40 °C. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the pyridinyl dibenzyl ester intermediate: ^{1}H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.0 (t, 2H), 4.1 (s, 1H), 5.4 (s, 4H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3-7.5 (m, 12H), 7.78 (s, 2H), 7.9 (d, 1H).

Step 4: Preparation of pyridinyl diacid

A suspension of 0.8813 g (0.99 mmole) of dibenzyl ester (obtained from Step 3) and 40 mg of 10% Pd/C in 35 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 143 °C; 1H NMR (THF-d8) 0.95 (q, 6H), 1.05-1.65 (m, 15H), 1.9 (m, 4H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 4.1 (s, 3H), 4.3 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.78 (d, 1H), 7.82 (s, 2H). HRMS. Calc'd for $C_{38}H_{50}N_2O_9S$: 711.3315. Found: 711.3322. Anal. Calc'd for $C_{38}H_{50}N_2O_9S$: C, 64.20; H, 7.09; N, 3.94; S, 4.51. Found: C, 62.34; H, 6.97; N, 4.01; S, 4.48.

Example 1422



(4R-cis)-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]guanidine

Step 1: Preparation of pentyl azide intermediate

To a stirred solution of 200 mg (0.328 mmol) of the pentyl bromide intermediate (obtained from Example 1420, Step 1) in 0.75 mL of DMSO was added 32 mg (0.493

mmol) of sodium azide and a catalytic amount of sodium iodide. The reaction was stirred at ambient temperature for 64 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 155 mg (92% RPHPLC purity, about 76% yield) of the pentyl azide intermediate as a colorless foam. Sample was used without further purification: mp 45-50 °C; ^1H NMR ($CDCl_3$) δ 0.83-0 93 (m, 6H), 1.03-1.48 (m, 10H), 1.54-1.74 (m, 5H), 1.78-1.86 (m, 1H), 2.14-2.26 (m, 1H), 2.81 (s, 6H), 3.06 (AB_q, J_{AB} = 15.0, 48.0 Hz, 2H), 3.31 (t, J = 6.3 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 4.09 (s, 1H), 5.47 (s, 1H), 6.10 (d, J = 1.8 Hz, 1H), 6.63 (dd, J = 2.7, 9.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H). MS (FAB, M+H) *m/e* 571.

Step 2: Preparation of pentyl amine intermediate

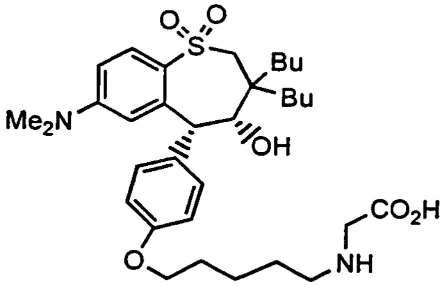
To a solution of 0.67 g (1.17 mmol) of the azide intermediate (obtained from Step 1) in 75 mL of ethanol was added 0.10 g of 10% palladium on carbon and the mixture shaken under 49 psi of hydrogen at ambient temperature for 3.5 hours. The reaction was filtered through celite and concentrated in vacuo to give 0.62 g (86% RPHPLC purity, ca. 84%) of pentyl amine intermediate as an off-white foam. The sample was used without further purification: mp 70-85 °C; ^1H NMR ($CDCl_3$) δ 0.86-0.96 (m, 6H), 1.06-1.75 (m, 15H), 1.79-1.93 (m, 4H), 2.15-2.28 (m, 1H), 2.82 (s, 6H), 2.96-3.20 (m, 4H), 3.99 (t, J = 6.0 Hz, 2H), 4.04-4.14 (m, 1H), 5.49 (s, 1H), 6.00 (d, J = 1.5 Hz, 1H), 6.51 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J =

8.1 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 1H). MS (ES, M+H) *m/e* 545.

Step 3: Preparation of guanidine

To a stirred solution of 258 mg (0.474 mmol) of pentyl amino intermediate (obtained from Step 2) and 81 mg (0.551 mmol) of 1H-pyrazole-1-carboxamidine hydrochloride in 1.5 mL of DMF was added 71 mg (0.551 mmol) of diisopropylethylamine. The reaction was stirred at ambient temperature for 16 hours. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 120 mg (43%) of the desired title compound as colorless foamy solid: mp 67.0-72.5 °C; 1H NMR ($CDCl_3$) δ 0.89-0.93 (m, 6H), 1.05-1.17 (m, 1H), 1.26-1.90 (m, 16H), 2.07-2.24 (m, 1H), 2.81 (s, 6H), 2.99-3.19 (m, 4H), 3.98 (br s, 2H), 4.12 (s, 1H), 5.46 (s, 1H), 6.01 (d, *J* = 2.1 Hz, 1H), 6.51 (dd, *J* = 2.1, 8.0 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* =8.7 Hz, 1H). HRMS. Calc'd for $C_{32}H_{50}N_4O_4S$:586.3552. Found(M+H): 587.3620.

Example 1423



(4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-

benzothiepin-5-yl]phenoxy]pentyl]glycine

Step 1: Preparation of pentyl azide intermediate

To a solution of pentyl bromide intermediate (400 mg, 0.657 mmol, obtained from Example 1420, Step 1) in dimethyl sulfoxide (20 mL) was added sodium azide (47 mg, 0.723 mmol, 1.1 eq), and the resulting clear solution was stirred at 23 °C for 16h. The reaction solution was diluted with 100 mL ethyl acetate, then washed with water (2x 100 mL) and brine (1x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 390 mg (quantitative) of pentyl azide intermediate as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.82-0.90 (m, 7H), 1.05-1.56 (m, 12H), 1.59-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.82 (s, 6H), 3.08 (q, 2H), 3.44 (t, J = 7.7 Hz, 2H), 3.99 (t, J = 7.7 Hz, 2H), 4.91 (br s, 1H), 5.47 (s, 1H), 6.13 (d, J = 7.58 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 7.14 (ABq, 4H), 7.91 (d, J = 7.8 Hz, 1H).

Step 2: Preparation of amino ester intermediate

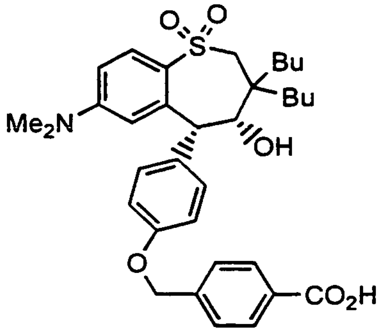
A suspension of pentyl azide intermediate (390 mg, 0.684 mmol, obtained from Step 1) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 4.5 hours. The ethanolic suspension was filtered through celite and concentrated in vacuo to give a yellow oil. The oil was immediately diluted with acetonitrile (15 mL), followed by the addition of triethylamine (0.156 g, 1.54 mmol, 2.25 eq) and bromo acetic acid benzyl ester (0.212 g, 0.925 mmol, 1.35 eq). The reaction was stirred at 23 °C for 48 hours. The reaction was concentrated in vacuo, and the residue was dissolved in ethyl acetate (20 mL) and washed with water (2x 20 mL) and brine (1x 20 mL). The organic layer was dried

($MgSO_4$) and dried in vacuo to give 420 mg (89%) of the amino ester intermediate as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.82-0.90 (m, 6H), 1.05-1.56 (m, 14H), 1.58-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, *J*= 8.3 Hz, 1H), 2.75 (d, *J* = 7.83 Hz, 1H), 2.795 (s, 6H), 3.08 (q, 2H), 3.68-3.85 (m, 2H), 3.87-4.04 (m, 2H), 4.09 (s, 1H), 5.147 (s, 1H), 5.46 (s, 1H), 5.98 (d, *J* = 7.58, 1H), 6.50 (dd, 1H), 6.85-6.87 (m, 2H), 7.28-7.45 (m, 5H), 7.89 (d, *J* = 8.0 Hz, 1H). MS (ES) *m/e* 693.

Step 3: Preparation of acid

A suspension of benzyl ester intermediate (0.420g, 0.61 mmol, obtained from Step 2) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 16h. The suspension was filtered through celite, and concentrated in vacuo to give 0.330g of a yellow semi-solid. The material was triturated with diethyl ether and the remaining semi-solid was dried in vacuo to give 0.19 g (52%) of the desired title compound as a yellow semi solid: ^1H NMR ($CDCl_3$) δ 0.86 (br s, 7H), 1.0-1.72 (m, 18H), 1.79 (br s, 2H), 1.98 (s, 2H), 2.09-2.24 (m, 2H), 2.78 (s, 6H), 2.99 (q, 2H), 3.96 (bs, 2H), 4.08 (s, 1H), 5.46 (s, 1H), 5.97 (s, 1H), 6.40-6.49 (m, 1H), 7.14 (ABq, 4H), 7.85 (t, *J* = 7.93 Hz, 1H). MS (ES) *m/e* 603.

Example 1424



(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]benzoic acid

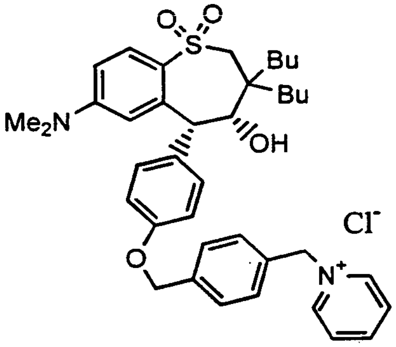
Step 1: Preparation of benzoate intermediate

To a solution of 0.53 g (1.15 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 10 mL dimethylformamide was added 35 mg (1.39 mmol) of 95% sodium hydride and stirred for 10 minutes. To the reaction mixture was added 525 mg (2.29 mmol) methyl 4-(bromomethyl)benzoate and stirred for 16 hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.51 g (73%) of the benzoate intermediate: ^{1}H NMR ($CDCl_3$) δ 0.86-0.96 (m, 6H), 1.14-1.47 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.23 (m, 1H), 2.80 (s, 6H), 2.99 (d, J = 15.1 Hz, 1H), 3.15 (t, J = 15.1 Hz, 1H), 3.92 (s, 3H), 4.09-4.15 (m, 1H), 5.17 (s, 2H), 5.49 (s, 1H), 5.94 (d, J = 2.2 Hz, 1H), 6.50 (dd, J = 8.9, 2.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H).

Step 2: Preparation of acid

A solution of 0.51 g (0.84 mmol) of the benzoate intermediate (obtained from Step 1) and 325 mg (2.53 mmol) of $KOSi(CH_3)_3$ (Aldrich) in 16 mL THF was stirred for 3.5 hours. The THF was evaporated, water added, extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.30 g (60%) of the desired title compound as a white solid: mp 156 - 159 °C; ^{1}H NMR ($CDCl_3$) δ 0.89-0.94 (m, 6H), 1.24-1.43 (m, 10H), 1.62-1.66 (m, 1H), 2.20-2.24 (m, 1H), 2.84 (s, 6H), 3.02 (d, *J* = 15.1 Hz, 1H), 3.17 (d, *J* = 15.1 Hz, 1H), 4.14 (s, 1H), 5.20 (s, 2H), 5.50 (s, 1H), 6.16 (s, 1H), 6.71 (d, *J* = 9.1 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 2H). HRMS. Calc'd for $C_{34}H_{44}NO_6S$: 594.2889. Found: 594.2913.

Example 1425



(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-pyridinium chloride

Step 1: Preparation of chlorobenzyl intermediate

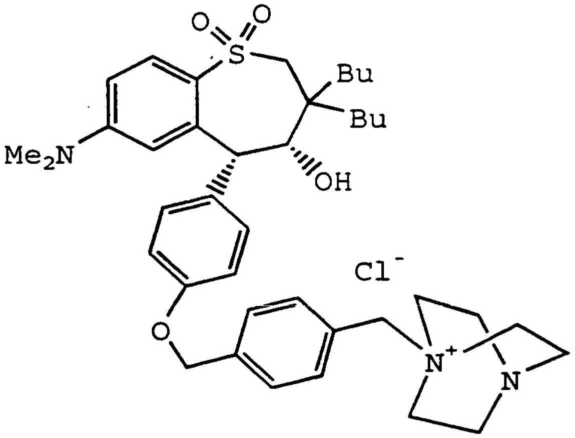
A solution of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N_2 was treated with powdered K_2CO_3 (2.3 g, 16.3 mmol, 1.5 eq.) and α,α′-dichloro-*p*-xylene (6.7 g, 38.1 mmol, 3.5 eq.) and the resulting solution was stirred at 65 °C for 48 hours. The reaction mixture was cooled to 25 °C and concentrated to 1/5 of original volume. The residue was dissolved in EtOAc (150 mL) and washed with water (2 x 150 mL). The aqueous layer was extracted with EtOAc (2 x 150 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 150 mL. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to provide a yellow oil. Purification by flash chromatography (5.4 x 45 cm silica, 25-40% EtOAc/hexane) afforded the chlorobenzyl intermediate (4.7 g, 72%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.89-0.94 (m, 6H), 1.12-1.48 (br m, 10H), 1.63 (m, 1H), 2.22 (m, 1H), 2.81 (s, 6H), 3.05 (ABq, *J* = 15.1 Hz, *J* = 50.0 Hz, 2H), 4.11 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 2H), 5.11 (s, 2H), 5.48 (s, 1H), 5.96 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, *J* = 8.9 Hz, 1H).

Step 2: Preparation of quaternary salt

A solution of the chlorobenzyl intermediate (1.0 g, 1.7 mmol, obtained from Step 1) in acetonitrile (5 mL) at 25 °C under N_2 was treated with pyridine (5 mL) and stirred at 35 °C for 36 hours. The pale amber solution was cooled to 25 °C and concentrated in vacuo to give the desired title compound (1.08 g, 96%) as a

yellow solid: mp 154-156 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 6H), 1.06-1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H), 2.71 (s, 6H), 3.02 (ABq, *J* = 15.1 Hz, *J* = 28.4 Hz, 2H), 4.09 (s, 1H), 5.00 (s, 2H), 5.38 (s, 1H), 5.91 (d, *J* = 2.4 Hz, 1H), 6.26 (s, 2H), 6.41 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, *J* = 7.7 Hz, 4H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.93 (t, *J* = 6.8 Hz, 1H), 8.34 (t, *J* = 7.7 Hz, 1H), 8.58 (br s, 1H), 9.69 (d, *J* = 5.8 Hz, 2H); HRMS. Calc'd for $C_{39}H_{49}N_2O_4S$: 641.3413. Found: 641.3425.

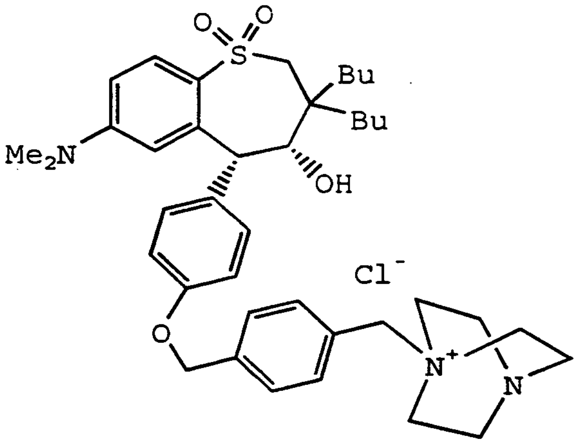
Example 1426



(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

Under N_2, a solution of 8.7 g (14.5 mmol) of the chlorobenzyl intermediate (obtained from a procedure similar to the one outlined in Example 1425, Step 1) in 60 mL of acetonitrile was added dropwise over a 30 min period to a solution of 2.9 g (26.2 mmol) of diazabicyclo[2.2.2]octane (DABCO) in 40 mL of acetonitrile at 35°C; during the addition, a colorless precipitate was formed. The slurry was stirred at 35°C for an additional 2 h. The product was collected and washed with 1 L of acetonitrile to give 9.6 g (93%) the title compound as a colorless crystalline solid: mp 223-230°C (decomposed); ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, *J* = 15.1 Hz, *J* = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, *J* = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for $C_{40}H_{56}N_3O_4S$: 674.3992. Found: 674.4005.

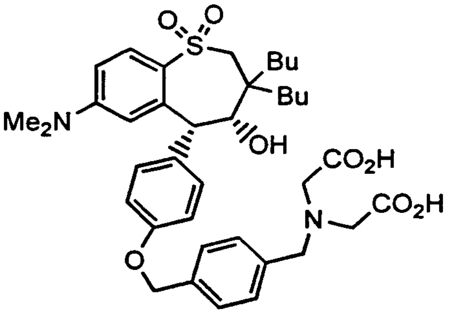
Example 1426a



(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

A solution of the chlorobenzyl intermediate (4.6 g, 7.7 mmol, obtained from Example 1425, Step 1) in acetonitrile (100 mL) at 25°C under N_2 was treated with diazabicyclo[2.2.2]-octane (DABCO, 0.95 g, 8.5 mmol, 1.1 eq.) and stirred at 35°C for 2 hours, during which time a white solid precipitated out. The white solid was collected, washed with CH_3CN and recrystallized from CH_3OH/Et_2O to give the title compound (4.95 g, 91%) as a white solid: mp 223-230°C (decomposed); ^1H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, J = 15.1 Hz, J = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for $C_{40}H_{56}N_3O_4S$: 674.3992. Found: 674.4005.

Example 1427



4R-cis)-N-(Carboxymethyl)-N-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-

yl]phenoxy]methyl]phenyl]methyl]glycine

Step 1: Preparation of chlorobenzyl intermediate

To a stirred solution of 144 mg (3.59 mmol, 60% disp) of NaH in 29 mL of DMF was added 1.5 g (3.26 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 45 min. To the solution was added 7.13 g (40.75 mmol) of dichloro p-xylene, and the mixture was stirred overnight. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the chlorobenzyl intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.1 (d, 1H), 4.6 (s, 2H), 5.1 (s,2H), 5.5 (s, 1H), 6.0 (s, 1H), 6.6 (d,1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.8 (d,1H).

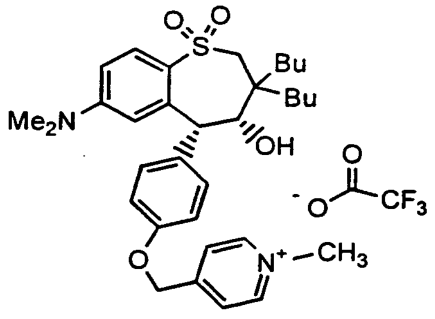
Step 2: Preparation of amino diester

A mixture of 1.03 g (1.72 mmol) of chlorobenzyl intermediate (obtained from Step 1), 1.63 g (8.6 mmol) of diethyl amino diacetate, and 0.72 g (8.6 mmol) of $NaHCO_3$ in 30 mL of DMF was stirred at 100 °C for 6 hours. DMF was removed in vacuo and the residue was extracted with ether and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give amino diester intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-1.65 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55 (s, 4H), 3.95 (s, 2H), 4.1-4.2 (m, 5H), 5.05 (s, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (s, 6H), 7.8 (d, 1H).

Step 3: Preparation of amino diacid

A solution of 0.863 g (1.15 mmol) of dibenzyl ester (obtained from Step 2) and 0.232 g (5.52 mmol) of LiOH in 30 mL of THF and 30 mL of water was stirred at 40 °C under N_2 for 4 hours. The reaction mixture was diluted with ether and washed with 1% HCl. The aqueous layer was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the desired title compound as a solid: mp 175 °C; ^{1}H NMR (THF-d8) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.5 (s, 4H), 3.9 (s, 2H), 4.1 (d, 1H), 5.1 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS. Calc'd for $C_{38}H_{50}N_2O_8S$: 695.3366. Found: 695.3359. Anal. Calc'd for $C_{38}H_{50}N_2O_8S$: C, 65.68; H, 7.25; N, 4.03; S, 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62.

Example 1428



(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium salt with trifluoroacetic acid (1:1)

Step 1: Preparation of picolyl intermediate

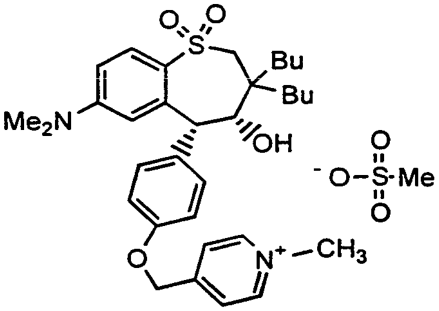
To a stirred solution of 12.0 g (26.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 200 mL of DMF was added 1.4 g (60% oil dispersion, 35 mmol) of sodium hydride and the reaction stirred at ambient temperature for one hour. 5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride was treated with cold saturated $NaHCO_3$ solution and extracted with diethyl ether. The ethereal extracts were washed with brine, dried over $MgSO_4$, and filtered. The reaction was cooled in an ice bath and the solution of 4-picolyl chloride in diethyl ether was added. The reaction was stirred at ambient temperature for 17 hours. The reaction was quenched with 25 mL of saturated NH_4Cl, diluted with 600 mL ethyl acetate washed with 4X250 mL water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-prep 500) using 60% ethyl acetate/hexanes afforded 11.05 g (77%) of the picolinyl intermediate as a colorless solid: mp 95-98 °C; ^1H NMR ($CDCl_3$) δ 0.86-0.96 (m, 6H), 1.02-1.52 (m, 10H), 1.58-1.70 (m, 1H), 2.16-2.29 (m, 1H), 2.81 (s, 6H), 3.07 (AB_q, J_{AB} = 15.3, 49.6 Hz, 2H), 4.10 (d, J = 7.5 Hz, 1H), 5.15 (s, 2H), 5.50 (s, 1H), 5.94 (d, J = 2.7 Hz, 1H), 6.51 (dd, J = 2.4, 8.7 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 7.39 (d, 6.0 Hz, 2H), 7.44 (s, J = 8.7 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 8.63 (dd, J = 1.6, 4.8 Hz, 2H).

Step 2: Preparation of quaternary salt

To a stirred solution of 0.41 g (0.74 mmol) of picolinyl intermediate (obtained from Step 1) in 10 mL of acetonitrile and 3 mL of dichloromethane was added

137 mg (0.97 mmol) of iodomethane. The reaction was stirred at ambient temperature for 16 hours, then concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60-55% water/acetonitrile afforded 0.304 g (60%) of the desired title compound as a colorless solid: mp 96-99 °C; ^{1}H NMR ($CDCl_3$) δ 0.85-0.95 (m, 6H), 1.03-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.27 (m, 1H), 2.84 (s, 6H), 3.09 (AB_q, J_{AB} = 15.0, 27.9 Hz, 2H), 4.11 (s, 1H), 4.46 (s, 3H), 5.37 (s, 2H), 5.50 (s, 1H), 6.07 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 2.5, 8.7 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 6.3 Hz, 2H), 8.80 (d, J = 6.6 Hz, 2H). HRMS Calc'd for $C_{33}H_{45}N_2O_4S$: 565.3100. Found: 565.3125.

Example 1429

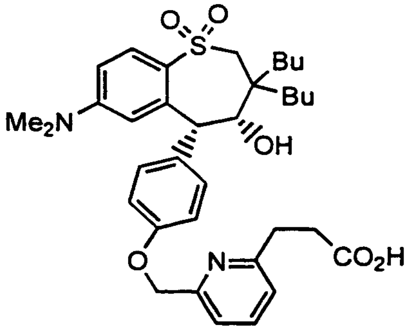


(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium, methanesulfonate (salt)

To a stirred solution of 6.5 g (11.8 mmol) of picolyl intermediate (obtained from Example 1428, Step

1) in 140 mL of acetonitrile heated at 70 °C was added 1.56 g (14.6 mmol) methanesulfonic acid methyl ester. Heating was continued at 70 °C for 15 hours. The reaction was cooled and diluted with 50 mL of ethyl acetate. The solid was collected by vacuum filtration to give 6.14 g (79%). The filtrate was concentrated _in vacuo_ and the residue crystallized from hot acetonitrile to give 1.09 g (14%). A total of 7.23 g (93%) of the desired title compound was obtained as an off-white solid: mp 232-233.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.66-0.76 (m, 6H), 0.85-0.95 (m, 1H), 0.95-1.35 (m, 9H), 1.42- 1.54 (m, 1H), 1.95-2.22 (m, 1H), 2.50 (s, 1H), 2.56 (s, 3H), 2.63 (s, 6H), 2.91 (AB_q, J = 16.5, 24.0 Hz, 2H), 3.88 (s, 1H), 4.40 (s, 3H), 5.21 (s, 3H), 5.78 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 2.5, 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.7 Hz, 1H), 8.0 (d, J = 6.6 Hz, 2H), 9.02 (d, J= 6.6 Hz, 2H). HRMS Calc'd for $C_{33}H_{45}N_2O_4S$: 565.3100. Found: 656.3087. Anal. Calc'd for $C_{34}H_{48}N_2O_7S_2$: C, 61.79; H, 7.32; N, 4.24; S, 9.70. Found: C, 61.38, H, 7.47; N, 4.22; S, 9.95.

Example 1430



(4R-cis)-6-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinepropanoic acid

Step 1: Preparation of picolinyl chloride intermediate

To a solution of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1g, 2.1 mmol, obtained from Example 1402, Step 10) in acetone (50 mL) was added anhydrous K_2CO_3 (0.45g, 3.2 mmol), tetrabutylammonium iodide (0.1g, 0.2 mmol) and 2,6-bischloromethylpyridine (1.2g, 10.8 mmol). The flask was equipped with nitrogen gas adapter and magnetic stirrer. The reaction was heated to reflux for overnight. After 18 hours, the reaction was diluted with ether and washed with water and brine (30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Chromatographic purification through silica gel, eluting with 25% EtOAc/Hexane gave 0.75 g (55%) of the picolyl chloride intermediate as an oil (0.70g, 55%): ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 4.10 (d, 2H), 4.65 (s, 2H), 5.20 (s, 2H), 5.45 (s, 1H), 5.95 (s, 1H), 6.50 (d, 1H), 7.0 (d, 2H),7.35-7.50 (m, 4H), 7.70-7.85 (m, 2H).

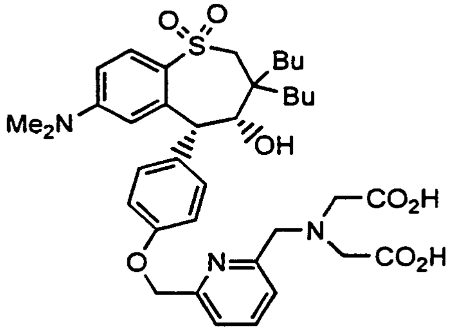
Step 2: Preparation of pyridinyl malonate intermediate

Dibenzyl malonate (1.42g, 5.01 mmol) in DMF (20.0 mL) and sodium hydride (0.13g, 3.3 mmol) were placed in a dry three-neck flask. The flask was equipped with nitrogen gas adapter and magnetic stirrer. The picolyl chloride intermediate (1g, 1.67 mmol) was added and heated at 90°C for overnight. The reaction was cooled and extracted with 5% HCl with methylene chloride and washed with water (25 mL), and brine (50 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by C-18 reversed phase column eluting with 50% acetonitrile/water and gave pyridinyl malonate intermediate as a white foamy solid (1g, 71%): ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.22 (d, 2H), 4.05 (d, 1H), 4.16 (t, 1H), 5.02(s, 2H), 5.08 (s, 4H), 5.44 (s, 1H), 5.97 (s, 1H), 6.96-7.10 (m, 3H), 7.20-7.32 (m, 12H), 7.5 (t, 1H), 7.9 (d, 1H).

Step 3: Preparation of pyridinyl acid

The pyridinyl malonate intermediate (0.6g, 0.7 mmol, obtained from Step 2), THF/water (25.0 mL, 1:1) and lithium hydroxide monohydrate (0.14 g, 3.4 mmol) were placed in a 100 mL round-bottom flask. The reaction was stirred at ambient temperature overnight. After 18 hours, the reaction was extracted with 1% HCl and ether and then washed with water (20 mL) and brine (30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* gave the desired title compound as a white solid (0.44g, 90%): mp 105-107 °C; ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H),3.05 (m, 2H), 3.10 (ABq, 2H), 3.22 (m, 2H), 4.05 (s, 1H), 5.30 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for $C_{35}H_{46}N_2O_6S$: 623.3155. Found: 623.3188.

Example 1431



(4R-cis)-N-(Carboxymethyl)-N-[[6-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinyl]methyl]glycine

Step 1: Preparation of pyridinyl diester intermediate

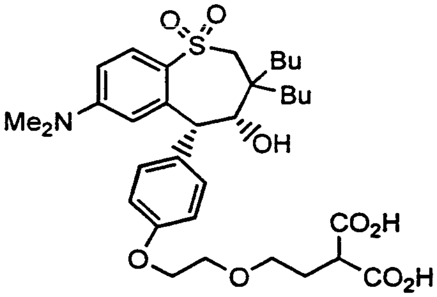
A mixture of diethyl aminodiacetate (8g, 68 mmol) and sodium carbonate (0.63g, 5.9 mmol) was treated with picolyl chloride intermediate (0.72g, 1.2 mmol, obtained from Example 1430, Step 1), and stirred at 160 °C for three hours. The reaction was cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by distillation in the Kugelrohr to give pyridinyl diester intermediate as a yellowish foamy solid (0.72g, 80%): ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 16H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.70 (s, 4H), 4.2-4.4 (m, 6H), 5.30 (s, 2H), 5.56 (s, 1H),6.02 (s, 1H), 6.60 (d, 1H), 7.10 (d, 2H),7.50 (m, 3H), 7.61 (d, 1H), 7.80 (t, 1H), 7.95 (d, 1H). HRMS. Calc'd for $C_{41}H_{57}N_3O_8S$: 752.3945. Found: 752.3948.

Step 2: Preparation of pyridinyl diacid

A mixture of pyridine-aminodiacetate intermediate (0.7g, 0.93 mmol, obtained from Step 1), and lithium hydroxide monohydrate (0.18 g, 4.5 mmol) in THF/ water (25.0 mL, 1:1) was stirred at 40 °C overnight (18 hours). The reaction mixture was diluted with ether and washed with 1% HCl, water (20 mL), and brine (30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give the desired title compound as a white solid (0.44g, 90%): mp 153-155 °C; ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H).

HRMS. Calc'd for $C_{37}H_{49}N_3O_8S$: 696.3319. Found:696.3331.

Example 1432



(4S-cis)-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethyl]propanedioic acid

Step 1: Preparation of bromoethyl ether intermediate

To a stirred solution of 0.192 g (4.785 mmol, 60% disp) of NaH in 28 mL of DMF was added 2.0 g (4.35 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 30 min. To the solution was added 13.2 g (54.38 mmol) of bis(2-bromoethyl)ether, and stirring was continued at ambient temperature under N_2 overnight. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give bromoethyl ether intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6h), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.5 (t, 2H), 3.9 (m, 4H), 4.1 (d, 1H), 4.2 (d, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.95 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

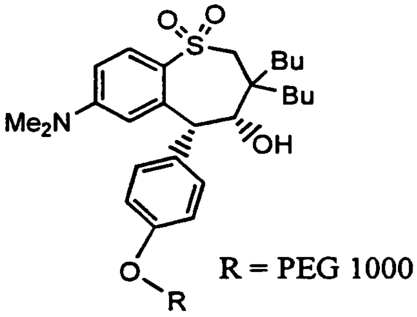
Step 2: Preparation of diester intermediate

To a mixture of 94 mg (2.34 mmol, 60% disp) of NaH in 45 mL of THF and 15 mL of DMF at 0 °C was added 1.33 g (4.68 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min, followed by the addition of 0.95 g (1.56 mmol) of bromoethyl ether intermediate (obtained from Step 1). The mixture was stirred under N_2 at 80 °C overnight. Solvent was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the diester intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2-2.3 (m, 3H), 2.8 (s, 6H), 3.0 (q, 2H), 3.6 (t, 2H), 3.7 (m, 3H), 4.1 (m, 3H), 5.1 (s, 4H), 5.42 (s, 1H), 5.9 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3 (m, 10H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 3: Preparation of diacid

A suspension of 0.761 g (0.935 mmol) of the diester intermediate (obtained from Step 2) and 35 mg of 10% Pd/C in 25 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 119.5 °C; ^{1}H NMR (THF-d8) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.1 (q, 2H), 2.25 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.47 (q, 2H), 3.58 (s, 1H), 3.78 (t, 2H), 4.08 (d, 1H), 4.15 (t, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.55 (d, 1H), 6.98 (d, 2H), 7.42 (d, 2H), 7.8 (d, 1H). HRMS. Calc'd for $C_{33}H_{47}NO_9S$: 632.2893. Found: 632.2882. Anal. Calc'd for $C_{33}H_{47}NO_9S$: C, 62.54; H, 7.47; N, 2.21; S, 5.06. Found: C, 61.75; H, 7.56; N, 2.13; S, 4.92.

Example 1433



(4R-cis)-a-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-w-methoxypoly(oxy-1,2-ethanediyl)

Step 1: Preparation of monomethyl PEG mesylate intermediate

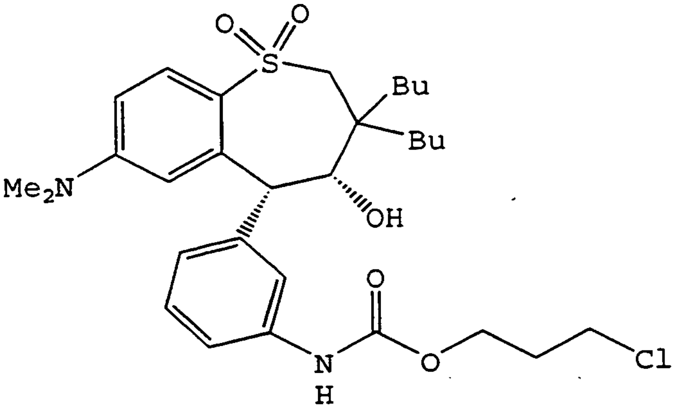
To a solution of 20 g of monomethyl ether PEG in 100 mL of methylene chloride was added 2.2 g (22 mmol) of triethyl amine, and to the resulting solution at 0°C was added dropwise 2.5 g (22 mmol) of methanesulfonyl chloride. The resulting solution was stirred overnight at ambient temperature, and the triethyl amine hydrochloride was filtered off to give the monomethyl PEG mesylate intermediate which was used in the next Step without further purification and characterization.

Step 2: Preparation of polyethylene-linked benzothiepene

A mixture of 38 mg (1.52 mmol 95%) of NaH and 0.7 g (1.52 mmol) of 5-(4′-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 5.5 mL of DMF was stirred at ambient temperature under N_2 for 30 min. To the solution was added 0.55 g (0.51 mmol) of the mesylate PEG intermediate (obtained from Step 1) in 5.5 mL of DMF, and the resulting solution was stirred overnight under N_2 at 50 °C. DMF was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the desired title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 0.9 (q, 6h), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 4H), 3.5-3.85 (m, 95H), 4.1 (s, 1H), 4.15 (t, 2H), 5.5 (s, 1H), 6.05 (s, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Example 1434

Preparation of:

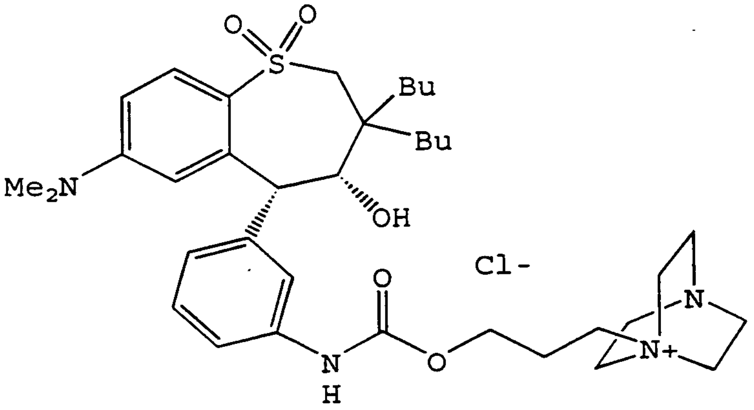


The 3-aminobenzothiepene prepared in Step 5 of Example 1398 (0.380g, 0.828 mmol), sodium hydroxide (0.35 mL, 0.875 mmol, 10% in H_2O) and toluene (0.50 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N_2, equipped with magnetic stirrer, and cooled to 0 °C. A solution of 3-chloropropyl chloroformate (1.440g, 1.10 mmol, 12% in CH_2Cl_2/ THF) was added. After 3.5 hrs, toluene (3.0 mL) was added, and the mixture was washed with H_2O (2x4 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20% EtOAc/hexane and concentrated *in vacuo* gave a white solid (0.269g, 56%). ^1H NMR (CDCl3) δ 0.87-0.93 (m, 6H), 1.05-1.70 (m, 11H), 2.14 (t, J = 6.3 Hz, 2H), 2.15-2.25 (m, 1H), 2.81 (s, 6H), 3.07 (ABq, 2H), 3.64 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 7.5 Hz, 1H), 4.33 (t, J = 6.0 Hz, 2H), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.7 Hz, 1H), 6.65 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.34-7.39 (m, 2H), 7.54 (d, J = 7.2 Hz, 1H), 7.89 (d, 8.7 Hz, 1H). HRMS (M +

H). Calc'd for $C_{30}H_{44}N_2O_5SCl$: 579.2659. Found: 579.2691.

Example 1435

Preparation of:

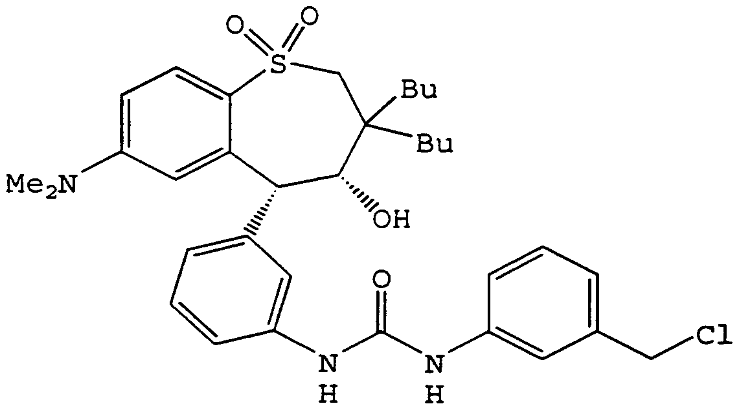


1,4-Diazabicyclo(2.2.2)octane (0.0785g, 0.700 mmol) and acetonitrile (1.0 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N_2, equipped with magnetic stirrer, and heated to 37 °C. A solution of the product of Example 1434 (0.250g, 0.432 mmol) in acetonitrile (2.50 mL) was added. After 2.5 hrs, 1,4-diazabicyclo(2.2.2)octane (0.0200g, 0.178 mmol) was added. After 64 hrs, 1,4-diazabicyclo(2.2.2)octane (0.0490g, 0.437 mmol) was added. After 24 hrs, the reaction mixture was cooled to R.T. and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (2.0 mL) and precipitated with ethyl ether (10.0 mL). The precipitate was filtered to yield a white solid. This trituration method was repeated, followed by concentrated *in vacuo* to give a white solid (0.185g, 62%). mp 218.0-225.0 °C; ^1H NMR (CD_3OD) δ 0.90 (m, 6H), 1.05-1.55 (m, 10H), 1.16 (t, J = 6.6 Hz, 2H), 1.78 (m, 1H), 2.12 (m, 3H), 2.76

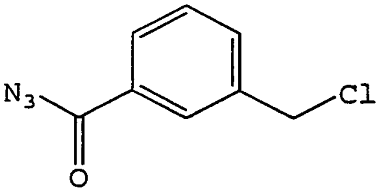
(s, 6H), 3.10 (m, 2H), 3.17 (t, J = 7.2 Hz, 6H), 3.30-3.50 (m, 8H), 4.10 (s, 1H), 4.21 (t, J = 5.4 Hz, 2H), 5.31 (s, 1H), 6.10 (s, 1H), 6.55 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 6.9 Hz, 1H), 7.33-7.42 (m, 2H), 7.56 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H). HRMS. Calc'd for $C_{36}H_{55}N_4O_5SCl$: 655.3893. Found: 655.3880.

Example 1436

Preparation of:



Step 1. Preparation of:



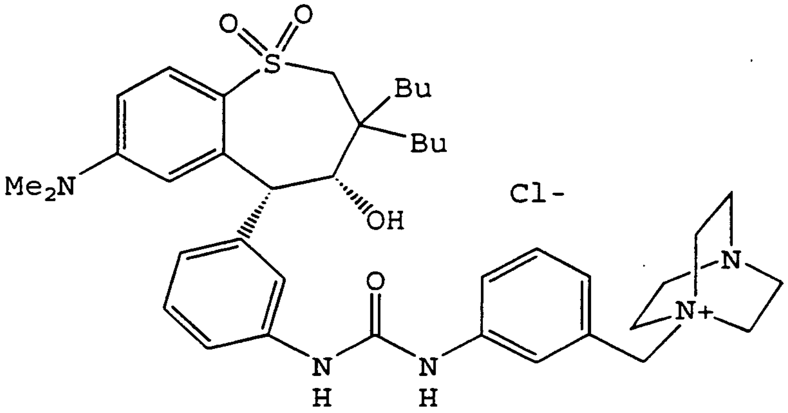
3-Chloromethylbenzoyl chloride (2.25 mL/15.8 mmol) and acetone (8.0 mL) were combined in a 25 mL round-bottom flask. The reaction flask was cooled to 0°C, and an aqueous solution of sodium azide (1.56g in 5.50 mL/24.0 mmol) was added. After 1.5 hrs, the reaction mixture was poured into ice water (80.0 mL), extracted with ethyl ether (2x25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a colorless oil (2.660g, 86%). ^1H NMR ($CDCl_3$) δ 4.62 (s, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H).

Step 2.

3-Chloromethylbenzoyl azide (0.142g, 0.726 mmol) and toluene (2.0 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N_2, equipped with magnetic stirrer, and heated to 110 °C. After 2 hrs, the reaction mixture was cooled to R.T, and the 3-aminobenzothiepene prepared in Step 5 of Example 1398 (0.365g, 0.796 mmol) was added. After 2.25 hrs, the mixture was heated to 50 °C. After 0.75 hrs, 3-chloromethylbenzoyl azide (0.025g, 0.128 mmol) was added, and the reaction mixture was heated to reflux. After 0.5 hrs, the reaction mixture was cooled to R.T. and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20-30% EtOAc/hexane and concentrated *in vacuo* gave a white foamy solid (0.309g, 62%). ^1H NMR ($CDCl_3$) δ 0.71 (t, J = 5.4 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H), 1.03-1.60 (m, 11H), 1.85 (d, 6.3 Hz, 1H), 2.27 (m, 1H), 2.76 (s, 6H), 3.15 (t, 2H), 4.17 (d, J = 6.6 Hz, 1H), 4.48 (s, 2H), 5.42 (s, 1H), 6.07 (s, 1H), 6.99 (d, J = 7.5 Hz), 7.18-7.26 (m, 2H), 7.30-7.41 (m, 3H), 7.63 (s, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 8.17 (s, 1H). HRMS (M + Li). Calculated for $C_{34}H_{44}N_3O_4SClLi$: 632.2901. Found: 632.2889.

Example 1437

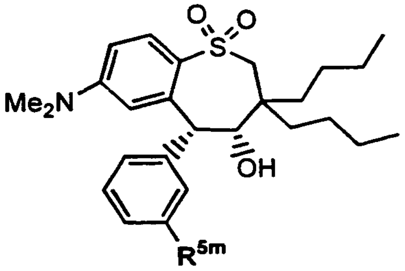
Preparation of:



1,4-Diazabicyclo(2.2.2)octane (0.157g, 1.40 mmol) and acetonitrile (1.00 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N_2 and equipped with magnetic stirrer. A solution of the product of Example 1436 (0.262g, 0.418 mmol) in acetonitrile (2.70 mL) was added. After 2.5 hrs, a white precipitate had had formed. Ethyl ether (6.0 mL) was added, and the precipitate was filtered, washed with ethyl ether, and dried *in vacuo* to yield a white solid (0.250g, 80%). mp 246.0-248.0 ^{o}C; ^{1}H NMR (CD_3OD) δ 0.88 (m, 6H), 1.03-1.55 (m, 10H), 1.76 (m, 1H), 2.11 (m, 1H), 2.74 (s, 6H), 3.11 (m, 8H), 3.37 (m, 6H), 4.12 (s, 1H), 4.39 (s, 2H), 5.31 (s, 1H), 6.11 (s, 1H), 6.52 (dd, J = 8.7, 1.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 6.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.47 (m, 2H), 7.58 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H). HRMS. Calculated for $C_{40}H_{56}N_5O_4SCl$: 702.4053. Found: 702.4064. Anal. Calculated for $C_{40}H_{56}N_5O_4SCl$: C, 65.06; H, 7.64; N, 9.48; S, 4.34; Cl, 4.80. Found: C, 64.90; H, 7.77; N, 9.42; S, 4.16; Cl, 4.89.

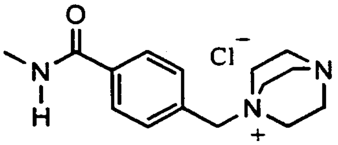
Examples 1438 - 1454

The compounds of Examples 1438 through 1454 can be prepared in accordance with one or more of the synthetic schemes previously disclosed in this application or using methods known to those skilled in the art.



R^{5m}

1438.



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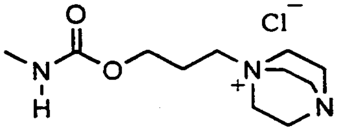

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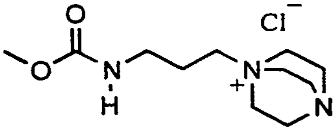

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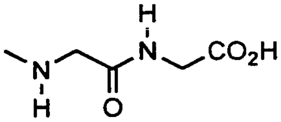

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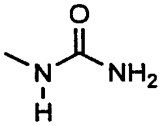

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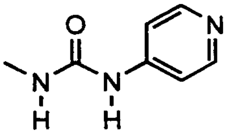

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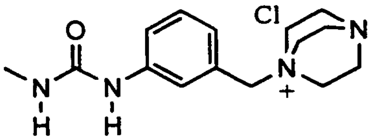

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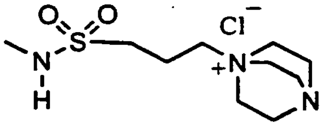

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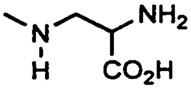
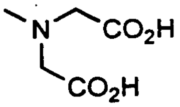
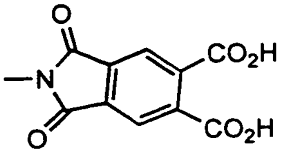
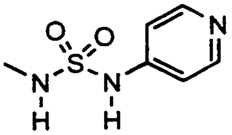
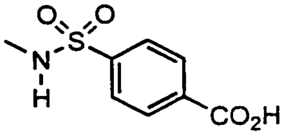


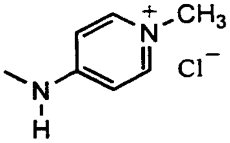
R^{5m}

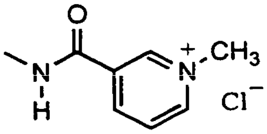
1446. 

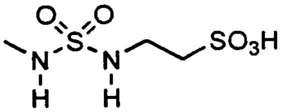
1447. 

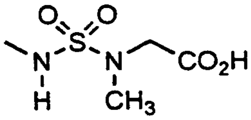
1448. 

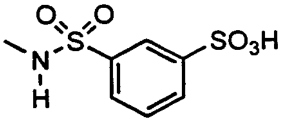
1449. 

1450. 

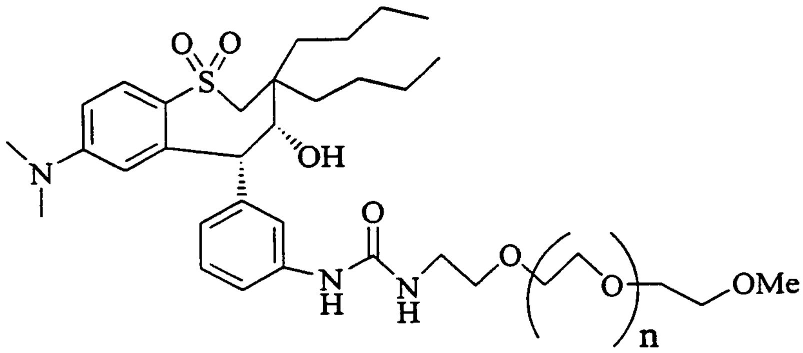
1451. 

1452. 

1453. 

1454. 

Example 1455



The 3-aminobenzothiepine of step 5 of Example 1398 (0.0165g/0.0360 mmol), M-NCO-5000 (0.150g/0.30 mmol) (Methoxy-PEG-NCO, MW 5000, purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), and $CDCl_3$ (0.7 mL) were combined in an 8 mm NMR tube. The tube was purged with N_2. After 72 hrs, the reaction mixture was heated to 50 °C. After 24 hrs, an additional aliquot of the 3-aminobenzothiepine of step 5 of Example 1398 (0.0077g/0.017 mmol) was added. After 24 hrs, the reaction mixture was transferred to a 2 mL vial and evaporated to dryness with a N_2 purge. The resulting white solid was dissolved in hot ethyl ether (2.0 mL) and ethyl acetate (0.057 mL/4 drops), cooled to precipitate and filtered. This precipitation procedure was repeated until no starting material was detected in the precipitate (TLC: SiO_2/80% EtOAc/hexanes). Concentrated *in vacuo* to give a white solid (0.0838g/51%). ^{1}H NMR (CDCl3) **d** 0.82-0.90 (m, 6H), 1.05-1.49 (m, 14H), 1.18 (t, J = 6.8 Hz, 2H), 1.59 (bt, 1H), 2.18 (bt, 1H), 2.34 (s, 2H), 2.78 (s, 6H), 3.04 (ABq, 2H), 3.35-3.80 (m, 625H), 4.09 (d, J = 7.2 Hz, 2H), 5.42 (s, 1H), 5.78 (s, 1H), 6.04 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 6.4, 3.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.31 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H). Mass spectroscopy data also verified desired product.

BIOLOGICAL ASSAYS

The utility of the compounds of the present invention is shown by the following assays. These assays are performed *in vitro* and in animal models essentially using a procedure recognized to show the utility of the present invention.

In Vitro Assay of compounds that inhibit IBAT-mediated uptake of $[^{14}C]$-Taurocholate (TC) in H14 Cells

Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded at 60,000 cells/well in 96 well Top-Count tissue culture plates for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours.

On the day of assay, the cell monolayer is gently washed once with 100 µl assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose + 0.2% (w/v) fatty acid free bovine serum albumin- (FAF)BSA). To each well 50 µl of a two-fold concentrate of test compound in assay buffer is added along with 50 µl of 6 µM $[^{14}C]$-taurocholate in assay buffer (final concentration of 3 µM $[^{14}C]$-taurocholate). The cell culture plates are incubated 2 hours at 37° C prior to gently washing each well twice with 100 µl 4° C

Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed once with 100 µl 4° C PBS without (FAF)BSA. To each 200 µl of liquid scintillation counting fluid is added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

***In Vitro* Assay of compounds that inhibit uptake of [^{14}C]-Alanine**

The alanine uptake assay is performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

***In Vivo* Assay of compounds that inhibit Rat Ileal uptake of [^{14}C]-Taurocholate into Bile**

(See"Metabolism of 3α,7β-dihydroxy-7α-methyl-5β-cholanoic acid and 3α,7β-dihydroxy-7α-methyl-5β-cholanoic acid in hamsters" in Biochimica et Biophysica Acta 833 (1985) 196-202 by Une et al.)

Male wistar rats (200-300 g) are anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (1/8" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum. A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum). 20 ml of warm Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). The proximal cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 min with warm PBS at 0.25 ml/min. Temperature of the gut segment is monitored continuously. At the start of the experiment, 2.0 ml of control sample ([^{14}C]-taurocholate @ 0.05 mi/ml with 5 mM cold taurocholate) is loaded into the gut segment with a 3 ml syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 ml/min for 21 min. Bile samples fractions are collected every 3 minute for the first 27 minutes of the procedure. After the 21 min of sample infusion, the ileal loop is washed out with 20 ml of warm PBS (using a 30 ml syringe), and then the loop is washed out for 21 min with warm PBS at 0.25 ml/min. A second perfusion is initiated as described above but this with test compound being administered as well (21 min administration followed by 21 min of wash out) and bile sampled every 3 min for the first 27 min. If necessary, a third perfusion is performed as above that typically contains the control sample.

Measurement of Hepatic Cholesterol Concentration (HEPATIC CHOL)

Liver tissue was weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant was separated and dried under nitrogen. The residue was dissolved in isopropanol and the cholesterol content was measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., *et al.* (1974) *Clin. Chem.* **20**, 470.

Measurement of Hepatic HMG CoA-Reductase Activity (HMG COA)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for HMG CoA reductase activity by incubating for 60 minutes at 37° C in the presence of ^{14}C-HMG-CoA (Dupont-NEN). The reaction was stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant was separated, by thin-layer chromatography, and the spot corresponding to the enzyme product was scraped off the plate, extracted and radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) *J. Lipid Res.* **31**, 2159).

Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)

Total serum cholesterol (SER.CHOL) was measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) was assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) were assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations were calculated as the difference between total and HDL cholesterol.

Measurement of Hepatic Cholesterol 7-α-Hydroxylase Activity (7a-OHase)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for cholesterol 7-α-hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent was evaporated and the residue was dissolved in acetonitrile/ methanol. The enzymatic product was separated by injecting an aliquot of the extract onto a C_{18} reversed phase HPLC column and quantitating the eluted material using UV detection at 240nm. (Reference: Horton, J. D., *et al.* (1994) *J. Clin. Invest.* **93**, 2084).

Rat Gavage Assay

Male Wister rats (275-300g) are administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% Tween 80 in water) is administered once a day (9:00-10:0 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight. Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described below. Compound efficacy is determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

Measurement of Fecal Bile Acid Concentration (FBA)

Total fecal output from individually housed hamsters was collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram was weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue was dissolved in methanol and the amount of bile acid present was measured enzymatically using the 3α-hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., *et al.* (1981) *Clin. Chem.* **27**, 1352).

[^{3}H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

Rabbit Ileal brush border membranes were prepared from frozen ileal mucosa by the calcium precipitation method describe by Malathi *et al.* (Reference: (1979) *Biochimica Biophysica Acta,* **554**, 259). The method for measuring taurocholate was essentially as described by Kramer *et al.* (Reference: (1992) *Biochimica Biophysica Acta,* **1111**, 93) except the assay volume was 200 µl instead of 100 µl. Briefly, at room temperature a 190 µl solution containing 2µM [^{3}H]-taurocholate(0.75 µCi), 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was incubated for 5 sec with 10 µl of brush border membrane vesicles (60-120 µg protein). The incubation was initiated by the addition of the BBMV while vortexing and the reaction was stopped by the addition of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 µm pore) and an additional 5 ml wash with stop buffer.

Acyl-CoA;cholesterol Acyl Transferase (ACAT)

Hamster liver and rat intestinal microsomes were prepared from tissue as described previously (Reference: (1980) *J. Biol. Chem.* **255**, 9098) and used as a source of ACAT enzyme. The assay consisted of a 2.0 ml incubation containing 24 µM Oleoyl-CoA (0.05 µCi) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 buffer containing 0.25 % BSA and 200 µg of microsomal protein. The assay was initiated by the addition of oleoyl-CoA. The reaction went for 5 min at 37° C and was terminated by the addition of 8.0 ml of chloroform/ methanol (2:1). To the extraction was added 125 µg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction were separated by centrifugation after thorough vortexing. The chloroform phase was taken to dryness and then spotted on a silica gel 60 TLC plate and developed in hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard instaimager.

Data from each of the noted compounds in the assays described above is as set forth in TABLES 5, 6, 7, and 8 as follows:

TABLE 5

COMPOUND	IC50 uM*	In vitro % Inhibition of TC Uptake @ 100 uM #	% Inhibition of Alanine Uptake @ 100 uM #	% of Control Transport of TC in Rat Ileum @ 0.1mM #
Benzothiazepine=	2		0	45.4 +/- 0.7
12		25		
3		0		
4a		3		
5a		34		
5b	40		0	72.9 ± 5.4 @ 0.5 mM
4b		9		
18		6		
14b		18		
14a		13		
13		23		
15	60			
19a		0		
19b		15		
8a		41		
Mixture of 8a and 8b		69		
Mixture of	6			

9a and 9b				
6a	5			
6b		85		
9a	5		0% @ 25 μM	53.7 +/- 3.9
Mixture of 6a and 20	13			
Mixture of 6d and 10a	0.8		14% @ 25 μM	
21a		37		
21c		52		
21b		45		
6c	2		58.5	68.8 +/- 5.7 at 0.4 mM
6d	0.6		77.7	16.1 +/- 1.1 @ 0.5 mM 30.2 +/- 0.9 @ 0.15 mM
17		10		
7	50		49.3	
10a	7		77.6	62.4 =/- 2.5 @ 0.2 mM
10b	15		68.6	
25	0.1		4% @ 10 μM	26.0 +/- 3.3
26	2		31% @ 25 μM	87.9 +/- 1.5
27	5		7% @ 20 μM	

28	8		31% @ 20μM	
29		88 @ 50 μM		
30		96 @ 50 μM		
31		41 @ 50 μM		
37	3		0% @ 5 μM	
38	0.3		11% @ 5μM	20.6 +/- 5.7
40		49 @ 50 μM		
41	2		0% @ 20 μM	
42	1.5			
43	1.5		16% @ 25 μM	
48	2		22% @ 20 μM	
49	0.15		21% @ 200 μM	21.2 +/- 2.7
57		51 @ 50 μM		
58		20 @ 50 μM		
59	70			
60	9		59	
61	30		175	
62	10			
63		90 @ 6 μM		

64		100 @ 6 μM		

* In vitro Taurocholate Cell Uptake

# Unless otherwise noted

= Comparative Example is Example No. 1 in WO 93/16055

TABLE 6

Compound	TC-uptake	TC-uptake	TC-uptake	ACAT	ACAT
	(H14 cells)	Ileal Loop	(BBMV)	(liver)	intestine
	IC(50)	EC(50)	IC(50)	IC(50)	IC(50)
COMP. EXAMPLE*	1 μM	74 μM	3 μM	20 μM	20 μM
6d	0.6 μM	31 μM	1.5 μM	25 μM	20 μM
* 38	0.3 μM	12 μM	2 μM	15 μM	N.D.
49	0.1 μM	12 μM	N.D.	6 μM	N.D.
25	0.1 μM	20 μM	0.8 μM	8 μM	8 μM

Comparative Example is Example No. 1 in WO 93/16055

TABLE 7

EFFICACY OF COMPOUND NO. 25 IN CHOLESTEROL-FED HAMSTERS

PARAMETER	CONTROL	4% CHOLESTYRAMINE	0.2% CPD. NO. 25
WEIGHT (G)	(mean ± SEM, *p<0.05, A-Student's t, B-Dunnett's)		
day 1	117 (2)	114(6)	117(5)
day 14	127(3)	127(3)	132(4)
LIVER WEIGHT (G)	5.4(0.3)	4.9(0.4)	5.8(0.2)
SER.CHOL(mg%)	143(7)	119(4)*A,B	126(2)*A,B
HDL-CHOL(mg%)	89(4)	76(3)*A,B	76(1)*A,B
VLDL + LDL	54(7)	42(3)*A	50(3)
TGI(mg%)	203(32)	190(15)	175(11)
HEPATIC CHOL(mg/g)	2.5(0.3)	1.9(0.1)*A,B	1.9(0.1)*A,B
HMG COA (pm/mg/min.)	15.8(7.6)	448.8(21.6)*A,B	312.9(37.5)*A,B
7a-OHase (pm/mg/min.)	235.3(25.1)	357.2(28.3)*A,B	291.0(6.0)*A
24 HR. FECAL Wt (G)	2.3(0.1)	2.7(0.1)*A,B	2.4(0.04)
FBA (mM/24H/100g)	6.2(0.8)	12.3(1.5)*A,B	11.9(0.5)*A,B

TABLE 8

EFFICACY OF COMPOUND NO. 25 IN RAT ALZET MINIPUMP MODEL

PARAMETER	CONTROL	20 MPL/DAY CPD. NO. 25
WEIGHT (G)	(mean ± SEM, *p<0.05, A-Student's t, B-Dunnett's)	
day 1	307 (4)	307 (3)
day 8	330 (4)	310 (4)*A,B
LIVER WEIGHT (G)	15.5 (0.6)	14.6 (0.4)
SER.CHOL(mg%)	85 (3)	84 (3)
HEPATIC CHOL(mg/g)	21 (0.03)	2.0 (0.03)
HMG COA pm/mg/min	75.1 (6.4)	318.0 (40.7)*A,B
7a-OHase (pm/mg/min)	281.9 (13.9)	535.2 (35.7)*A,B
24 HR. FECAL WT (G)	5.8 (0.1)	5.7 (0.4)
FBA (mM/24H/100g)	17.9 (0.9)	39.1 (4.5)*A,B

Additional *in vitro* taurocholate uptake tests were conducted in the following compounds listed in Table 9.

Table 9
Biological Data for Some Compounds of the Present Invention

Compound Number	Human TC IC_{50} (µM)	Alanine Uptake Percent Inhibition @ µM
101		0 @ 1.0
102	0.083	
103		13 @ 0.25
104	0.0056	
105	0.6	
106	0.8	
107		14.0 @ 0.063
108	0.3	
109		2.0 @ 0.063
110	0.09	
111	2.5	
112	3.0	
113	0.1	
114	0.19	
115	8.0	
116	0.3	
117		12.0 @ 0.625
118	0.4	
119	1.3	
120		34.0 @ 5.0
121	0.068	
122	1.07	
123	1.67	
124		14.0 @ 6.25
125	18.0	
126		18 @ 1.25
127	0.55	
128	0.7	
129	0.035	
131	1.28	
132		5.4 @ 0.063
133	16.0	
134	0.3	
135	22.0	
136	0.09	
137	2.4	
138	3.0	
139	>25.0	
140		

141		
142	0.5	
143	0.03	
144	0.053	
262	0.07	
263	0.7	
264	0.2	
265	2.0	
266	0.5	
267	0.073	
268	0.029	
269	0.08	
270	0.12	
271	0.07	
272	0.7	
273	1.9	
274	0.18	
275		5.0 @ 0.25
276	0.23	
277	0.04	
278	3.0	
279	0.4	
280	0.18	
281	0.019	
282	0.021	
283	0.35	
284	0.08	
285		
286	19.0	
287	4.0	
288		10.0 @ 6.25
289	0.23	
290	0.054	
291	0.6	
292	0.046	
293	1.9	
294	0.013	
295	1.3	
296	1.6	
1000		
1001		
1002		
1003		
1004		
1005	0.0004	
1006	0.001	
1007	0.001	
1008	0.001	
1009	0.001	

1010	0.001	
1011	0.001	
1012	0.0015	
1013	0.002	
1014	0.002	
1015	0.002	
1016	0.002	
1017	0.002	
1018	0.002	
1019	0.002	
1020	0.002	
1021	0.002	
1022	0.002	
1023	0.002	
1024	0.002	
1025	0.002	
1026	0.002	
1027	0.002	
1028	0.002	
1029	0.002	
1030	0.002	
1031	0.002	
1032	0.002	
1033	0.002	
1034	0.002	
1035	0.002	
1036	0.002	
1037	0.0022	
1038	0.0025	
1039	0.0026	
1040	0.003	
1041	0.003	
1042	0.003	
1043	0.003	
1044	0.003	
1045	0.003	
1046	0.003	
1047	0.003	
1048	0.003	
1049	0.003	
1050	0.003	
1051	0.003	
1052	0.003	
1053	0.003	
1054	0.003	
1055	0.003	
1056	0.003	
1057	0.003	
1058	0.003	

1059	0.003	
1060	0.0036	
1061	0.004	
1062	0.004	
1063	0.004	
1064	0.004	
1065	0.004	
1066	0.004	
1067	0.004	
1068	0.004	
1069	0.004	
1070	0.004	
1071	0.004	
1072	0.004	
1073	0.004	
1074	0.004	
1075	0.0043	
1076	0.0045	
1077	0.0045	
1078	0.0045	
1079	0.005	
1080	0.005	
1081	0.005	
1082	0.005	
1083	0.005	
1084	0.005	
1085	0.005	
1086	0.005	
1087	0.005	
1088	0.0055	
1089	0.0057	
1090	0.006	
1091	0.006	
1092	0.006	
1093	0.006	
1094	0.006	
1095	0.006	
1096	0.006	
1097	0.006	
1098	0.006	
1099	0.0063	
1100	0.0068	
1101	0.007	
1102	0.007	
1103	0.007	
1104	0.007	
1105	0.007	
1106	0.0073	
1107	0.0075	

1108	0.0075	
1109	0.008	
1110	0.008	
1111	0.008	
1112	0.008	
1113	0.009	
1114	0.009	
1115	0.0098	
1116	0.0093	
1117	0.01	
1118	0.01	
1119	0.01	
1120	0.01	
1121	0.01	
1122	0.011	
1123	0.011	
1124	0.011	
1125	0.012	
1126	0.013	
1127	0.013	
1128	0.017	
1129	0.018	
1130	0.018	
1131	0.02	
1132	0.02	
1133	0.02	
1134	0.02	
1135	0.021	
1136	0.021	
1137	0.021	
1138	0.022	
1139	0.022	
1140	0.023	
1141	0.023	
1142	0.024	
1143	0.027	
1144	0.028	
1145	0.029	
1146	0.029	
1147	0.029	
1148	0.03	
1149	0.03	
1150	0.03	
1151	0.031	
1152	0.036	
1153	0.037	
1154	0.037	
1155	0.039	
1156	0.039	

1157	0.04	
1158	0.06	
1159	0.06	
1160	0.062	
1161	0.063	
1162	0.063	
1163	0.09	
1164	0.093	
1165	0.11	
1166	0.11	
1167	0.12	
1168	0.12	
1169	0.12	
1170	0.13	
1171	0.14	
1172	0.14	
1173	0.15	
1174	0.15	
1175	0.17	
1176	0.18	
1177	0.18	
1178	0.19	
1179	0.19	
1180	0.2	
1181	0.22	
1182	0.25	
1183	0.28	
1184	0.28	
1185	0.28	
1186	0.3	
1187	0.32	
1188	0.35	
1189	0.35	
1190	0.55	
1191	0.65	
1192	1.0	
1193	1.0	
1194	1.6	
1195	1.7	
1196	2.0	
1197	2.2	
1198	2.5	
1199	4.0	
1200	6.1	
1201	8.3	
1202	40.0	
1203		0 @ 0.063
1204	0.05	
1205	0.034	

1206	0.035	
1207	0.068	
1208	0.042	
1209		0 @ 0.063
1210	0.14	
1211	0.28	
1212	0.39	
1213	1.7	
1214	0.75	
1215	0.19	
1216	0.39	
1217	0.32	
1218	0.19	
1219	0.34	
1220	0.2	
1221	0.041	
1222	0.065	
1223	0.28	
1224	0.33	
1225	0.12	
1226	0.046	
1227	0.25	
1228	0.038	
1229	0.049	
1230	0.062	
1231	0.075	
1232	1.2	
1233	0.15	
1234	0.067	
1235	0.045	
1236	0.05	
1237	0.07	
1238	0.8	
1239	0.035	
1240	0.016	
1241	0.047	
1242	0.029	
1243	0.63	
1244	0.062	
1245	0.32	
1246	0.018	
1247	0.017	
1248	0.33	
1249	10.2	
1250	0.013	
1251	0.62	
1252	29.	
1253	0.3	
1254	0.85	

1255	0.69	
1256	0.011	
1257	0.1	
1258	0.12	
1259	16.5	
1260	0.012	
1261	0.019	
1262	0.03	
1263	0.079	
1264	0.21	
1265	0.24	
1266	0.2	
1267	0.29	
1268	0.035	
1269	0.026	
1270	0.026	
1271	0.011	
1272	0.047	
1273	0.029	
1274	0.028	
1275	0.024	
1276	0.029	
1277	0.018	
1278	0.017	
1279	0.028	
1280	0.76	
1281	0.055	
1282	0.17	
1283	0.17	
1284	0.011	
1285	0.027	
1286	0.068	
1287	0.071	
1288	0.013	
1289	0.026	
1290	0.017	
1291	0.013	
1292	0.025	
1293	0.019	
1294	0.011	
1295	0.014	
1296	0.063	
1297	0.029	
1298	0.018	
1299	0.012	
1300	1.0	
1301	0.15	
1302	1.4	
1303	0.26	

1304	0.25	
1305	0.25	
1306	1.2	
1307	3.1	
1308	0.04	
1309	0.24	
1310	1.16	
1311	3.27	
1312	5.0	
1313	6.1	
1314	0.26	
1315	1.67	
1316	3.9	
1317	21.0	
1318		
1319		11.0 @ 0.25
1320		
1321		11.1 @ 5.0
1322		3.0 @ 0.0063
1323		4.0 @ 0.0063
1324		43.0 @ 0.0008
1325		1.0 @ 0.0063
1326		36.0 @ 0.0008
1327		3.0 @ 0.0063
1328		68.0 @ 0.0063
1329		2.0 @ 0.0063
1330		9.0 @ 0.0063
1331		57.0 @ 0.0008
1332		43.0 @ 0.0008
1333		0 @ 0.0063
1334		50.0 @ 0.0008
1335		38.0 @ 0.0008
1336		45.0 @ 0.0008
1337		0 @ 0.0063
1338		1.0 @ 0.25
1339		0 @ 0.063
1340		9.0 @ 0.063
1341		1.0 @ 0.063
1342		1.0 @ 0.063
1343		
1344		
1345		13.0 @ 0.25
1346		
1347	0.0036	
1348		
1349		
1350		
1351	0.44	
1352	0.10	

1353	0.0015	
1354	0.006	
1355	0.0015	
1356	0.22	
1357	0.023	
1358	0.008	
1359	0.014	
1360	0.003	
1361	0.004	
1362	0.019	
1363	0.008	
1364	0.006	
1365	0.008	
1366	0.015	
1367	0.002	
1368	0.005	
1369	0.005	
1370	0.002	
1371	0.004	
1372	0.004	
1373	0.008	
1374	0.007	
1375	0.002	
1449	0.052	
1450	0.039	
1451	0.014	

Additional *in vitro* taurocholate uptake tests and *in vivo* rat gavage tests were conducted on the following compounds listed in Tables 10 and 11.

TABLE 10

In Vitro Taurocholate Uptake Assay Data for Some Additional Compounds of the Present Invention

Compound of Example Number	Human TC IC50 (nM)
1402	25
1403	23
1404	10
1405	21
1406	4
1407	3
1408	1
1409	0.9
1410	2
1411	2
1412	3
1413	3
1414	15
1415	2
1416	14
1417	2
1418	<1
1419	3
1420	11
1421	4
1422	3
1423	3
1424	14
1425	2
1426	0.3
1427	2
1428	0.7
1429	
1430	3
1431	5
1432	26
1433	67

TABLE 11

Rat Gavage Assay Data for Some Additional Compounds of the Present Invention

Compound of Example No.	Study No.	Dose (mg/kg/day)	Delta (micromoles fecal bile acid per day)
1402	28	5 .2 .04	58.2 1.3 0.3
1402	30	2 .4 .08 .016	50.3 40.9 48.5 22.9
1403	30	2 .4 .08 .016	41.6 35.2 11.9 3
1404	28	5 .2 .04	93.7 59.1 33.5
1406	32	2 .4 .08 .016	47.8 31.6 12.8 -8.5
1407	32	2 .4 .08 .016	51.9 30.1 27.5 6.4
1407	33	2 .4 .08 .016	35 12.7 -.04 -4.5
1408	29	2 .4 .08 .016	41.2 36.8 16.8 -3.3
1408	37	2 .4 .08 .016	26.2 45.2 26.3 6.6
1409	33	2 .4 .08 .016	19.2 28.7 14.1 -1.7
1409	41	2 .4 .08	44.2 35.9 14.5

		.016	11
1410	33	32.4	
		34.3	
		27.9	
		9.3	
1410	35	2	26.2
		.4	36.5
		.08	18.5
		.016	20.4
1411	34	2	63.4
		.4	54.1
		.08	33
		.016	22.3
1413	26	5	52.3
		.2	42.4
		.04	19
1414	27	5	45.2
		.2	39.5
		.04	14.3
1414	31	2	41.5
		.4	33.7
		.08	29
		.016	3.8
1415	28	5	59.9
		.2	48.1
		.04	23.9
1415	37	2	48.9
		.4	25.7
		.08	27.1
		.016	12.7
1416	29	2	46.1
		.4	21.9
		.08	25
		.016	-7.8
1417	31	2	51.4
		.4	42
		.08	39.6
		.016	29.3
1418	29	2	20.3
		.4	29.5
		.08	-4.6
		.016	-10
1419	31	2	28.5
		.4	13.9
		.08	10.3
		.016	5.8
1420	31	2	53.1
		.4	45
		.08	38.1
		.016	29.6
1421	32	2	57.8

		.4 .08 .016	27.7 25.3 4.7
1423	34	2 .4 .08 .016	56.5 69.3 35.3 14.4
1425	21	5 .2 .04	91.8 100. 66.4
1425	30	2 .4 .08 .016	44.6 62 69.5 31.6
1425	40	2 .4 .08 .016	48.3 45 31.2 30
1426	33	2 .4 .08 .016	52.4 19.5 23.1 24.6
1426	35	2 .4 .08 .016	37.7 41.7 40.5 24.6
1426	39	2 .4 .08 .016	54.3 48.7 51.8 26.8
1426	43	2 .4 .08 .016	40.8 21.7 5.9 4.1
1427	40	2 .4 .08 .016	36.7 35.8 27.3 13.8
1428	34	2 .4 .08 .016	40.4 64.9 24.4 12.2
1428	42	2 .4 .08 .016	46 40.7 26 1.1
1429	41	2 .4 .08	34.5 24.9 18.7

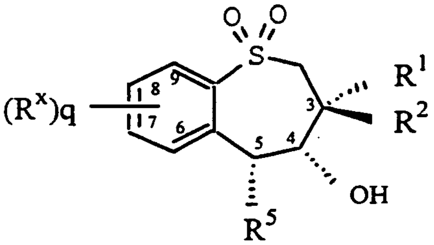
		.016	9.2
1429	42	2 .4 .08 .016	47.1 31.1 35.5 4.8
1430	30	2 .4 .08 .016	51.2 50.4 20.7 -5.6
1431	32	28.3 45.8 21.9 1.1	
1432	28	5 .2 .04	36.2 9.7 2.4
1433	24	20 2 .2	66.5 47.4 26.5

The examples herein can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Novel compositions of the invention are further illustrated in attached Exhibits A and B.

The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

Exhibit A
Table C2: Alternative Compounds #2 (Families F101-F123)



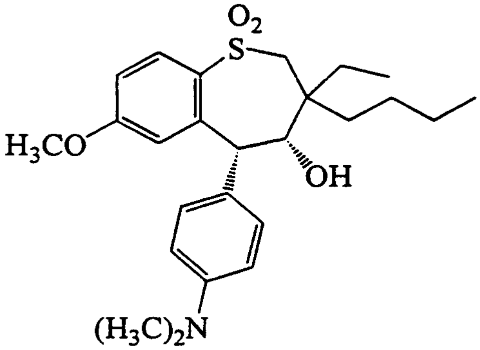
Family	Cpd #	$R^1=R^2$	R^5	$(R^x)q$
F101		CHOSEN FROM TABLE 1	Ph-	CHOSEN FROM TABLE 1
F102		CHOSEN FROM TABLE 1	p-F-Ph-	CHOSEN FROM TABLE 1
F103		CHOSEN FROM TABLE 1	m-F-Ph-	CHOSEN FROM TABLE 1
F104		CHOSEN FROM TABLE 1	p-CH_3O-Ph-	CHOSEN FROM TABLE 1
F105		CHOSEN FROM TABLE 1	m-CH_3O-Ph-	CHOSEN FROM TABLE 1
F106		CHOSEN FROM TABLE 1	p-$(CH_3)_2N$-Ph-	CHOSEN FROM TABLE 1
F107		CHOSEN FROM TABLE 1	m-$(CH_3)_2N$-Ph	CHOSEN FROM TABLE 1
F108		CHOSEN FROM TABLE 1	I^-, p-$(CH_3)_3$-N^+-Ph-	CHOSEN FROM TABLE 1
F109		CHOSEN FROM TABLE 1	I^-, m-$(CH_3)_3$-N^+-Ph-	CHOSEN FROM TABLE 1

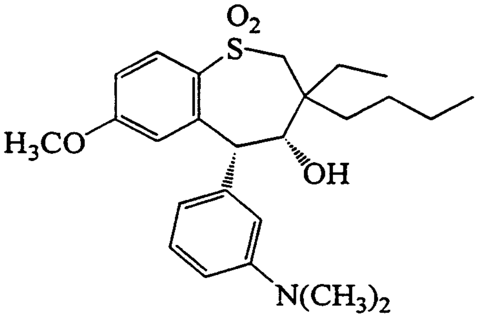
F110		CHOSEN FROM TABLE 1	I^-, p-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE 1
F111		CHOSEN FROM TABLE 1	I^-, m-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE 1
F112		CHOSEN FROM TABLE 1	I^-, p-(N,N-dimethylpiperazine)-(N′)-CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE 1
F113		CHOSEN FROM TABLE 1	I^-, m-(N,N-dimethylpiperazine)-(N′)-CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE 1
F114		CHOSEN FROM TABLE 1	m-F-Ph- p-CH_3O-	CHOSEN FROM TABLE 1
F115		CHOSEN FROM TABLE 1	3,4,dioxy-methylene-Ph-	CHOSEN FROM TABLE 1
F116		CHOSEN FROM TABLE 1	m-F-Ph- p-F-Ph-	CHOSEN FROM TABLE 1
F117		CHOSEN FROM TABLE 1	m-CH_3O- p-F-Ph-	CHOSEN FROM TABLE 1
F118		CHOSEN FROM TABLE 1	4-pyridine	CHOSEN FROM TABLE 1
F119		CHOSEN FROM TABLE 1	N-methyl-4-pyridinium	CHOSEN FROM TABLE 1
F120		CHOSEN FROM TABLE 1	3-pyridine	CHOSEN FROM TABLE 1
F121		CHOSEN FROM TABLE 1	N-methyl-3-pyridinium	CHOSEN FROM TABLE 1

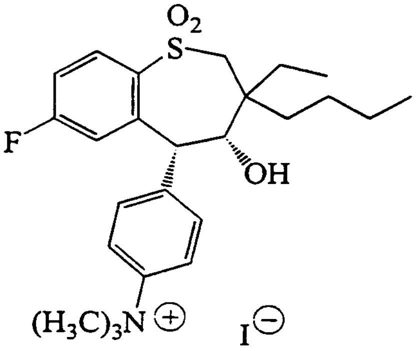
F122		CHOSEN FROM TABLE 1	2-pyridine	CHOSEN FROM TABLE 1
F123		CHOSEN FROM TABLE 1	p-CH_3O_2C-Ph-	CHOSEN FROM TABLE 1

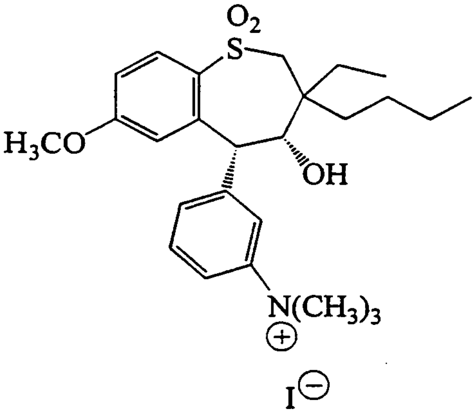
Similar families can be generated where R^1 is not equal to R^2, such as R^1 = Et and R^2 = n-Bu, but $(R^x)q$ is chosen from table C1.

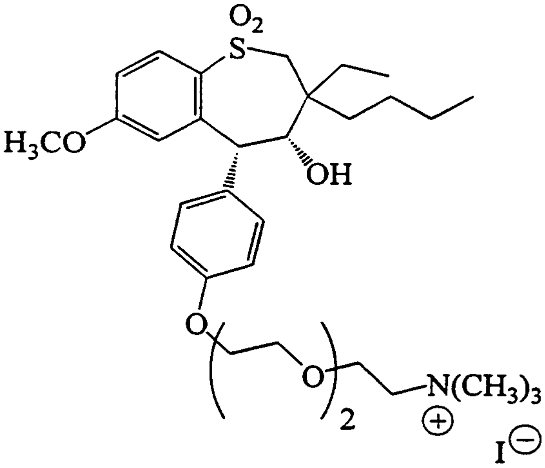
Exhibit B

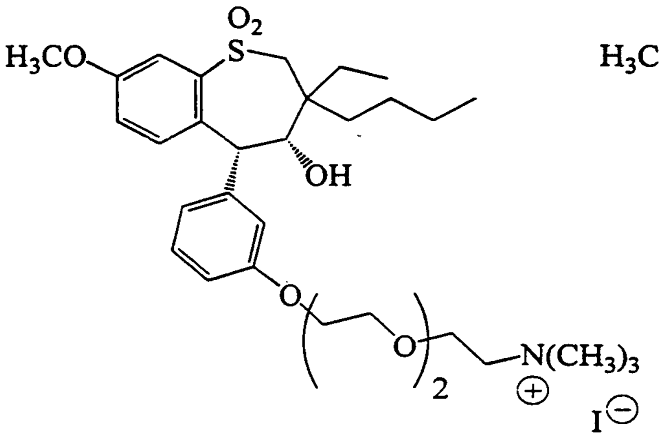

O2
S
H3CO
OH
(H3C)2N

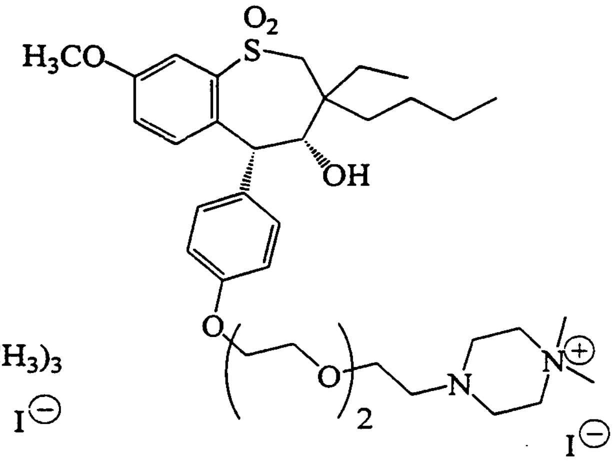

O2
S
H3CO
OH
N(CH3)2

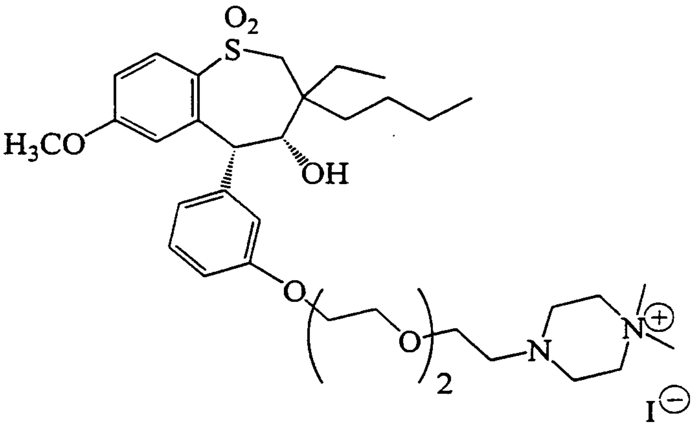

O2
S
F
OH
(H3C)3N ⊕
I ⊖

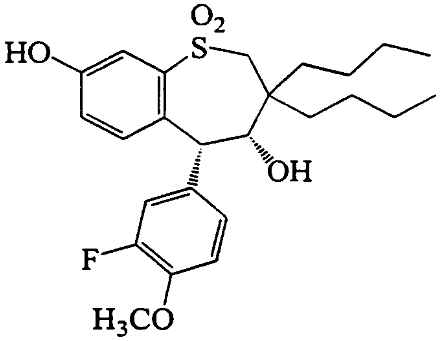

O2
S
H3CO
OH
N(CH3)3
⊕
I ⊖

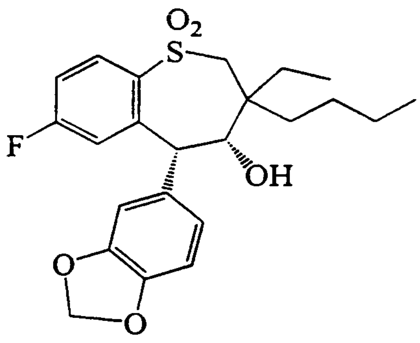

O2
S
H3CO
OH
O
O
2
N(CH3)3
⊕
I ⊖

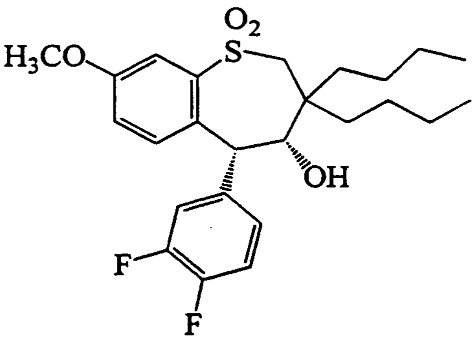


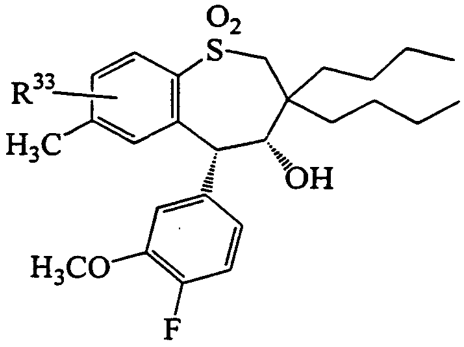


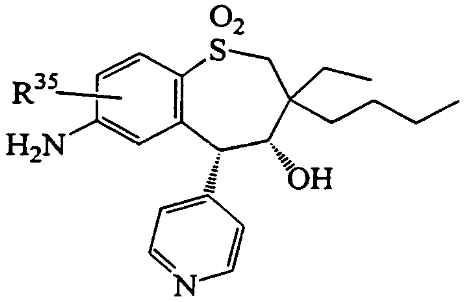


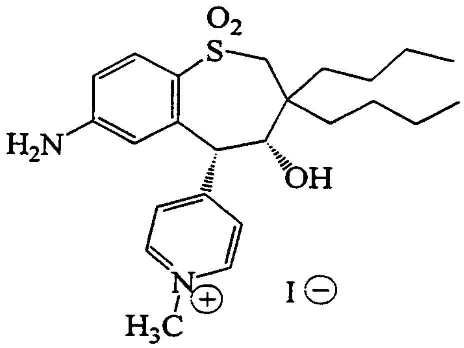


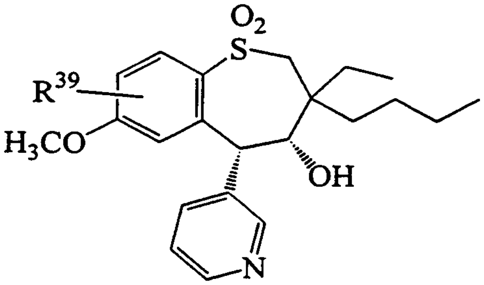


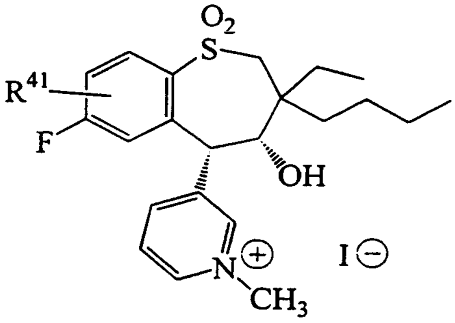


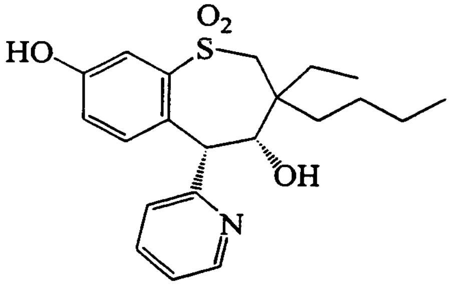

O2
S
R33
H3C
OH
H3CO
F


O2
S
R35
H2N
OH
N


O2
S
H2N
OH
N
+
H3C
I −


O2
S
R39
H3CO
OH
N


O2
S
R41
F
OH
N
+
CH3
I −


O2
S
HO
OH
N